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LEPRECHAUNISM

A EUPHUISM FOR A RARE FAMILIAL DISORDER

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WHEN a new term for a disease complex is proposed, particularly if the suggestion is more fanciful than scientific, an apology or at least an explanation should accompany the introduction.

In 1948, one of us (W. L. D.) reported an unusual syndrome under the rather inappropriate title "dysendocrinism."[1] This concerned a female infant with peculiar elfinlike facies, hirsutism, and multiple endocrine abnormalities. At that time the literature was routinely searched and no report of a similar case was found. Because of the prominence of the bizarre endocrine disturbances, the rather nondescript and colorless term "dysendocrinism" was applied. This designation was unfortunate as it had no specific connotation and did not draw attention to the peculiar external appearance of the infant.

Interest in this syndrome was reawakened when a second child, born into the same family and exhibiting the same stigmas, came under observation in The Hospital for Sick Children.

During the course of correspondence concerning these two unusual infants the name "leprechaunism" was suggested as a fitting designation.[2] As these unfortunate creatures had more the appearance of caricatures than of true human beings, and because of the complex nature of the disturbances present, which made academic terminology difficult to apply, the term "leprechaunism" for the syndrome seemed most apt and found favor locally.

As no accurate or definitive description of a leprechaun is available, there may be serious and valid objections to the identification of the appearance of these infants with that of a leprechaun. There is agreement, however, that leprechauns were, originally at least, indigenous to Ireland. The consensus is that they are little hairy sprites, although some authorities maintain in addition that they are male and green. Although it may be argued that our cases do not fulfill all the suggested descriptive requirements of a leprechaun, with a little imagination the term can be as suitably applied to the syndrome encountered in these two infants as the terms gargoylism, cretinism (little Christian) and mongolism, which are common usage.

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FAMILY HISTORY

The father, J. S., and the mother, M. S., were first cousins once removed. A genetic analysis will be given below. Both were of Anglo-Saxon descent and have always been normal and healthy. The two affected infants, Charlotte S. and Irene S. were the result of the mother's first and seventh pregnancies. Mrs. S. was 28 years of age at the time of her first pregnancy. The following limited investigations were done on both parents: basal metabolic rate glucose tolerance tests, and x-rays of skull and hands. All of these were within normal limits.

Obstetrical History of Mrs. S.—In Table I are listed the results of the seven pregnancies of Mrs. S. No significant information could be elicited in regard to the two abortions and one miscarriage. The pregnancies and deliveries associated with the two normal living children were not unusual. During the mother's first pregnancy which resulted in Charlotte, her abdominal enlargement ceased at approximately the seventh month, and even regressed to such a degree that her friends asked whether or not she had delivered her child. Intrauterine fetal movements were barely detectable from this time. At term there was a medical, followed by a surgical, induction. In the mother's last pregnancy which brought forth Irene, regression in the abdominal mass was also noted beginning about the seventh month. This last pregnancy was terminated at seven and one-half months by cesarean section, because of pre-eclampsia and possible placenta previa.

CASE REPORTS

CASE 1.—Charlotte S., born March 22, 1947, died May 7, 1947, age 46 days.

History.—The baby's birth weight was 3 pounds 14 ounces. She had one cyanotic attack shortly after birth. Subsequently her progress was slow. At 20 days of age she was noted to have shallow respirations and frequent attacks of cyanosis. Her abdomen became distended and a few red subcutaneous lumps appeared over the body and extremities which proved to be abscesses. Due to failure to gain, various feedings were tried with no improvement. The infant was admitted to The Hospital for Sick Children at 27 days of age, at which time her weight had decreased to 3 pounds.

Physical Examination.—The infant was an underdeveloped and poorly nourished female with an unusual facial appearance. The eyes were widely spaced and prominent, the ears large and low-set, and the hair abundant, giving the face a peculiar elfin appearance. The skin was loose, lying in folds, and there was obvious muscular wasting. Both the skin and

TABLE I.

First pregnancy	female	Charlotte S., born March 22, 1947, died May 7, 1947. *Leprechaunism.*
Second pregnancy	abortion	July, 1947.
Third pregnancy	abortion	December, 1947.
Fourth pregnancy	female	R. S., born Feb. 21, 1949. Alive and normal.
Fifth pregnancy	male	D. S., born June 29, 1950. Alive and normal.
Sixth pregnancy	miscarriage	November, 1951, at 4 months.
Seventh pregnancy	female	Irene S., born April 1, 1953, died June 8, 1953. *Leprechaunism.*

hair were dry. Hydration was fair but there was scanty subcutaneous fat. There were several red raised areas which were soft and freely movable and varied in size up to 2 cm. in diameter over the scalp, forehead, and back. The cranial sutures were separated. There were no signs of respiratory infection or cardiovascular abnormalities. The umbilicus was covered with a dry crust and the surrounding skin was slightly infected. The border of the liver was barely palpable. Both kidneys were palpated and each appeared to be the size of a small lemon. The clitoris was moderately hypertrophied.

Laboratory Examination. — Urine revealed a trace of albumen with occasional red blood cells and white blood cells. On two occasions sugar was found in the urine but this may have been due to intravenous therapy. Examination of the blood showed red blood cells 5.4 million, white blood cells 16.3 thousand, hemoglobin 15.8 grams per cent; blood film normal. Nonprotein nitrogen was 29.0 mg. per cent, creatinine 0.75 mg. per cent. Urine culture revealed bacilli of colon group. Blood culture was negative.

X-ray Investigations.—Two excretory urograms were unsuccessful due to a large amount of gas in the stomach and small bowel. The chest films were interpreted as showing emphysema, bronchiolitis, and interstitial pneumonitis. The skull showed increased width of the sutures which was considered as being due to retarded bony maturation.

Treatment and Progress.—The subcutaneous abscesses cleared satisfactorily with intramuscular penicillin therapy. The infant took feedings well and there was a slight weight gain. She was discharged on the sixteenth hospital day, at 7½ weeks of age, as she was considered to be free from infection. She was readmitted the following day because of coughing. During the short period at home she had two attacks of cyanosis. Her condition on readmission was as before except that there was a rough systolic murmur along the left border of the sternum. The infant's condition rapidly deteriorated for no obvious reason and she died two days following her readmission at 46 days of age.

The clinical diagnosis was dystrophy, progeria, multiple congenital malformation of head, face, heart, and kidneys, with possible gargoylism.

Case 2.—Irene S., born April 1, 1953, died June 8, 1953, age 69 days.

History.—This infant's birth weight was 3 pounds 8 ounces. She was maintained in an incubator in the maternity hospital from the time of the cesarean section until transfer to The Hospital for Sick Children. During this time she was fed by gavage but failed to gain. Oxygen was administered intermittently. She was difficult to hydrate and received numerous interstitials and two blood transfusions. Because of an elevated temperature and the development of "boils" or subcutaneous abscesses on the right upper extremity and behind her left ear, the infant received penicillin and Chloromycetin with no appreciable beneficial effect. Because of the persistent failure to thrive she was transferred to this hospital at 66 days of age. Her weight at this time was the same as her birth weight.

Physical Examination.—The infant was emaciated and dystrophic with a peculiar facial appearance similar to that of her sister. The skin was mottled and she appeared chronically ill. The fontanel was large and somewhat full. Bilateral masses could be felt in each flank which were presumed to be kidneys. Moderate hypertrophy of the labia and clitoris was present. The temperature on admission was 101° F.

Treatment and Progress.—A blood culture was taken which proved negative. Because of the precarious condition of the infant, no investigative procedures were done. Protein milk was used as a feeding. The temperature showed extreme lability, fluctuating between 101° and 95° F. She

was maintained in an incubator and oxygen was required. Death occurred three days after admission.

Clinical diagnosis was gargoylism, dystrophy, and possible septicemia.

PATHOLOGY

Because these two sisters had so obviously been cast in the same undersized, C. S. measuring 45 cm. in length and I. S. measuring 47 cm. Both at the time of death were approximately their birth weight: C. S. 3 pounds 10 ounces and I. S. 3 pounds 14 ounces. The degree of underdevelopment was remarkably uniform in both of these infants in spite

Figs. 1 and 2.—First infant, Charlotte S., at 6 weeks of age. The emaciation, peculiar facies, large ears, and breast changes are well shown.

usual mold, the findings in the post mortems of both Charlotte S. (A.122/47) and Irene S. (A.159/53) will be described concurrently.

External Stigmas.—The body of each was extremely emaciated and unof the fact that the first, C. S., was stated to have gone to full term and the second, I. S., was delivered by cesarean section at seven and one-half months' gestation. The peculiar and unusual facies was a characteristic

feature (Figs. 1, 2, 3, 4 and 5). The hair on the head was dark brown, fine, and abundant. The usual hairline was present at the forehead but in addition fine downy hair was present over the forehead, extending as low as the eyebrows. Anterior to the ears the hair extended low on the cheeks and fine hair was present in the beard area. Excessive lanugo was present over most of the body but there was no pubic hair. The external ears were large and low-set. The eyes were large, prominent, and widely spaced. The nose was retuse, broad at the tip with flaring nostrils. The mouth was large, with thick prominent Negroid lips. In each child the mammae were enlarged and the nipple was prominent. Under each nipple was a firm disclike mass measuring approximately 2.5 cm. in diameter and 1 cm. in thickness. In both, the abdomen was distended. There was abnormal prominence of the clitoris and the labia minor. This was accentuated by the degree of emaciation, but there is little doubt that there was some hypertrophy of the clitoris. Residuals of the subcutaneous abscesses were not detectable in C. S. but were present in I. S.

Figs. 3, 4, and 5.—Second infant, Irene S. Photographs taken after death. The unusual facial appearance and the hirsutism are particularly well shown in Figs. 4 and 5.

Fig. 4.—*For legend, see previous page.*

Fig. 5.—*For legend, see previous page.*

Gross Examination.—Most of the viscera of these infants were smaller than would be expected for the age of the patient but were probably in keeping with the growth retardation and emaciation. The following are the weights of various organs of Charlotte and Irene, respectively, all of which appeared grossly normal: thymus 2 grams, 1.3 grams; heart 16 grams, 16 grams; lungs—right 25 grams, left 18 grams, right 20 grams, left 16 grams; pancreas 4 grams, 3 grams; spleen 7 grams, 4.5 grams; adrenals each 2 grams, 1.3 grams, 1.4 grams. The alimentary tracts were not unusual.

The liver in each infant was small: C. S. 62 grams, I. S. 55 grams. They were of usual consistency, dark brownish red, and of normal contour. Scattered over the surface and throughout the substance of Charlotte's liver were numerous small pale grayish-yellow nodules measuring 2 to 3 mm. in diameter. These were flush with the surface of the liver. Grossly they were not unlike miliary tubercles. These were also present in Irene's liver but not nearly as prominent. The gall bladder and bile ducts were not unusual. The kidneys in both cases were enlarged to approximately twice normal size. In Charlotte each weighed 36 grams and in Irene 25 grams. They were brownish red, of normal contour, and there was no evidence of hydronephrosis. The capsules stripped easily. The cut surface revealed the cortex and medulla to be of normal relative width. The cortical markings were not blurred. In each case the collecting tubules in the pyramids were streaked with deposits of grayish-green material flecked with yellow. Both ovaries in each infant were tremendously enlarged, each measuring approximately 3 cm. in the long axis. The uteri and tubes were slightly enlarged but appeared otherwise normal. The head and brain including the pituitary appeared normal.

Microscopic Examination.—Here again the abnormal findings in each case were strikingly similar in all essential details. The photomicrographs herein reproduced are from the first case, Charlotte. Identical lesions were present in Irene.

Lungs: In both cases there was a moderate edema and a nonspecific terminal bronchopneumonia.

Liver: The alterations in the livers were most unusual. Scattered throughout the parenchyma, having no relationship with either the central or portal vein areas, were sharply circumscribed patches in which there were changes in the liver cells, which were in marked contrast to the remainder of the parenchyma (Fig. 6). In these areas the liver cells were swollen, their cell boundaries indistinct, and in some places there had been fusion of several liver cells with clumping of nuclei to form syncytial masses (Fig. 7). An additional change was extreme foamy vacuolization of the cytoplasm of the liver cells without displacement of the nuclei from the central position (Fig. 8). Differential stains revealed the presence of large deposits of glycogen in the cytoplasm of these foamy cells with minimal amounts in the cells of the liver outside these areas. Fat was present only in minimal amounts both in these foci and in other parts of the liver. Although jaundice was not obvious clinically or at post mortem in either case, many of the bile

canaliculi in all parts of the liver tissue contained plugs of inspissated bile. There were heavy deposits of iron pigment in both the liver cells and Kupffer cells of the intervening areas of liver, but not in the focal areas. These iron deposits were particularly prominent in the second case. A most unusual feature was the reciprocal relationship between the deposition of glycogen and iron pigment: much glycogen and no iron in the focal areas and the reverse in the remainder of liver tissue.

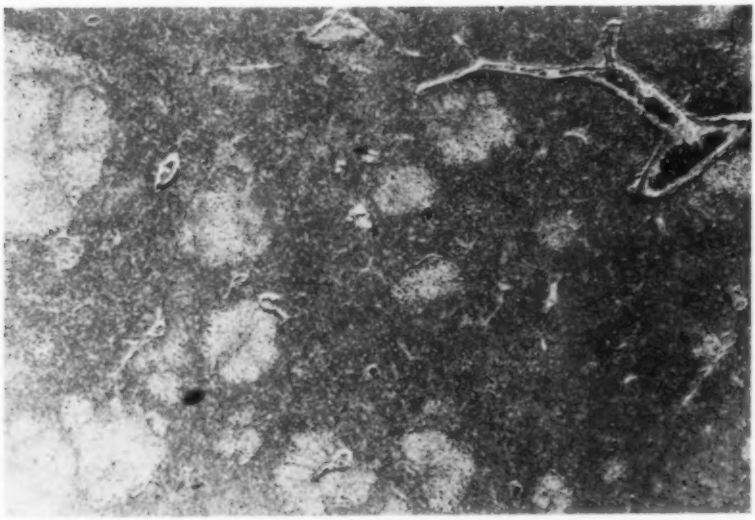


Fig. 6.—Photomicrograph (low power)—liver. The pale areas are the patchy foci of alteration in the liver cells.

Pancreas: The pancreas exhibited a tremendous increase in number and hyperplasia of the islets of Langerhans (Figs. 9 and 10). No mitotic figures were seen in either the islet or acinar tissue. Differential stains on the islet tissue revealed that the beta cells were the predominating type, although the granulations in these appeared somewhat deficient. A similar alteration was not detected in the less numerous alpha cells. A bioassay of the insulin content of the pancreas of the second case, Irene, was done by Dr. G. A. Wrenshall of the Banting and Best Department of Medical Research. This indicated a content of 26.8 units per gram of wet weight which was more than six times the upper limit of normal for this age group (approximately 4 units).

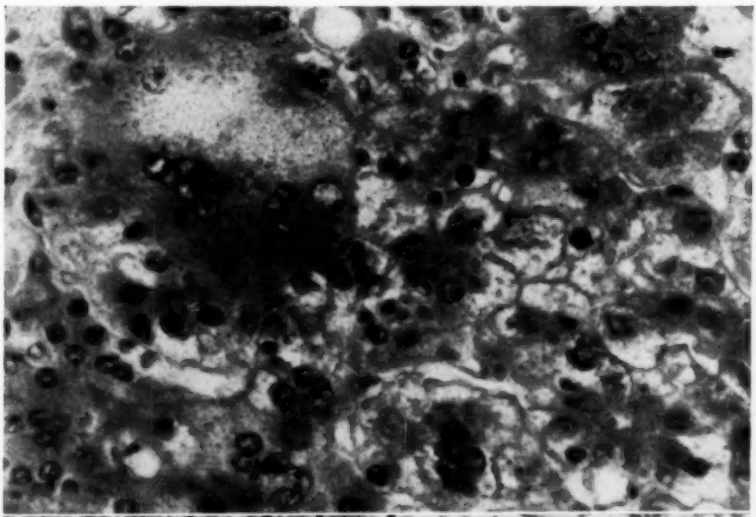
Ovaries: The ovaries in both cases showed marked follicular maturation and cyst development without evidence of luteinization (Figs. 11 and 12). Microscopically the uterus and tubes were not unusual.

Breast Tissue: Duct hyperplasia with early cyst formation was present in the breasts of both cases (Fig. 13). There was no evidence of acinar development.

Pituitary: Minimal histologic changes in the pituitary were difficult

to appraise. There was an impression that there was a definite increase in the number of basophils but those present appeared normal. There was no suggestion of hyalinization. The relative number of chromophobes and

Fig. 7.



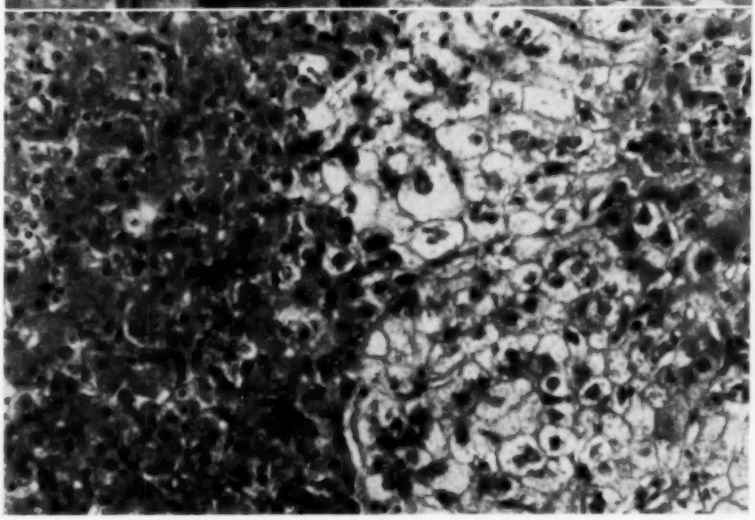


Fig. 8.

Fig. 7.—Photomicrograph (medium power)—liver. The center of one of the peculiar focal areas in the liver. There is fusion of liver cells to form syncytial masses with clumping of the nuclei.

Fig. 8.—Photomicrograph (medium power)—liver. Margin of one of the foci in the liver showing its sharp demarcation and the foamy vacuolated character of the cytoplasm of the liver cells in these areas.

eosinophils appeared to be within normal limits. Some of the eosinophils showed depletion or possible exhaustion of their granules.

Thymus: In routine post-mortem material, varying degrees of prominence and distention of Hassall's corpuscles is a common finding. How-

Fig. 9.

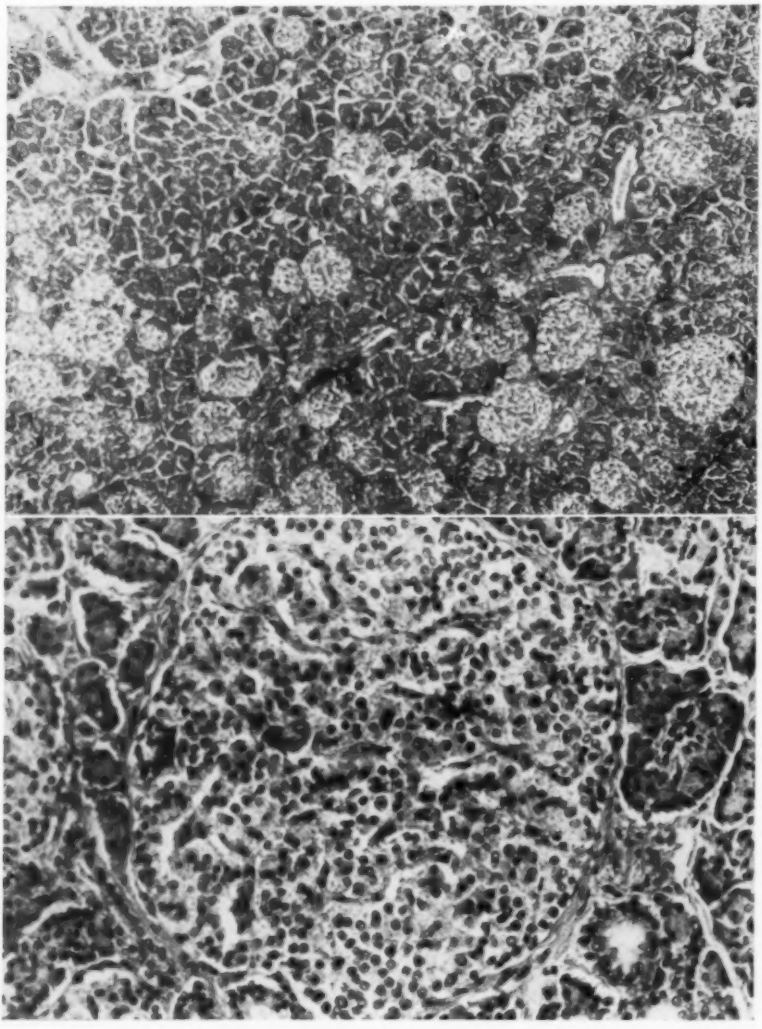


Fig. 10.

Fig. 9.—Photomicrograph (low power)—pancreas. The increase in number and size of the islets of Langerhans is obvious.

Fig. 10.—Photomicrograph (medium power)—pancreas. This demonstrates the hyperplasia of the islet tissue.

ever, in both of these cases this change was especially prominent. Under low power the tissue had a "Swiss cheese" appearance. Many of the distended corpuscles had coalesced. Most contained a granular coagulum, calcified debris, and numerous laminated psammous bodies (Fig. 14). There was atrophy of the lymphoid tissue.

Other Endocrine Glands: In neither case were significant histologic changes seen in the other endocrine

Fig. 11.

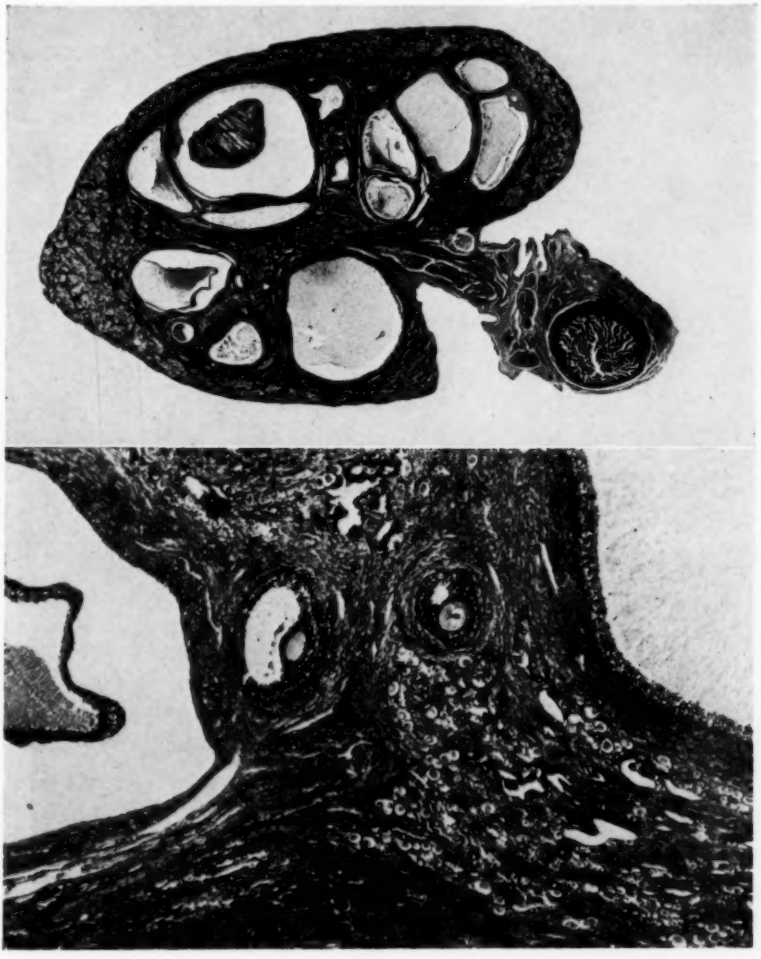


Fig. 12.

Fig. 11.—Photomicrograph (very low power)—ovary. A cross section of ovary including the Fallopian tube. Note the large number of follicular cysts.

Fig. 12.—Photomicrograph (medium power)—ovary. In the center are two developing follicles, each containing an ovum.

glands. The adrenals were small and normal for the age of the infants. The thyroids were normal. In neither infant were the parathyroids identified in the gross. However, in each case one parathyroid gland was found on microscopic examination in the tissue surrounding the thyroid. These were histologically normal and did not appear to be enlarged.

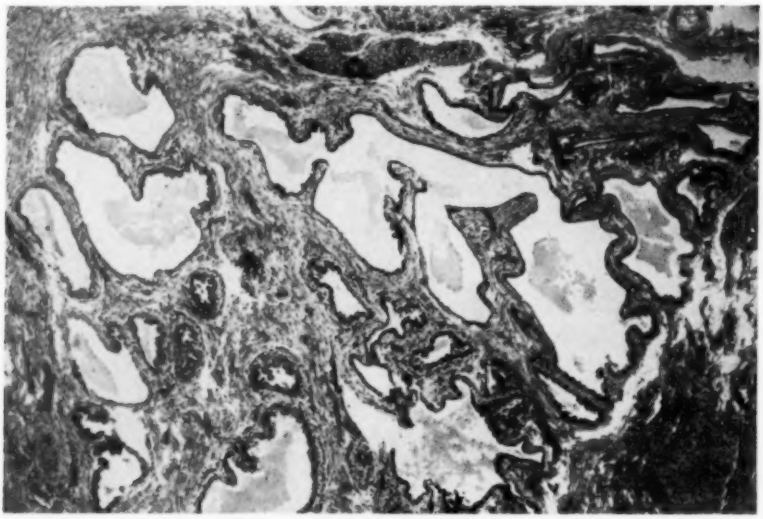


Fig. 13.—Photomicrograph (low power)—breast. This shows increase in the size of the ducts with hyperplasia of the duct epithelium and cyst formation. There is no evidence of developing acinar tissue.

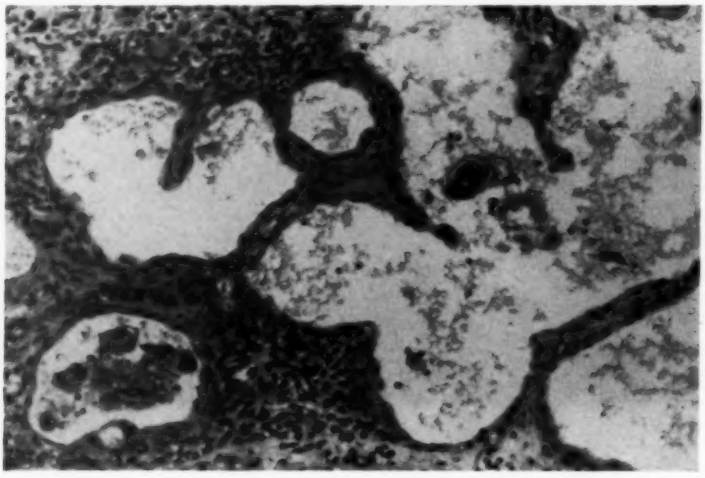


Fig. 14.—Photomicrograph (medium power)—thymus. Distention and "cystlike" formations of Hassall's corpuscles.

Kidneys: The kidneys in both infants exhibited diffuse dilatation of the tubules particularly marked in the collecting tubules. Aside from this there was no obvious lesion to explain the large size of the kidneys. The dilatation of the tubules was caused by conglomerate masses of a granular material plugging the collecting tubules (Fig. 15). This substance stained unevenly with a hematoxylin. Differential stains showed these masses to contain calcium. Iron was not present. Due to improper fixation, stains for urates were not done.

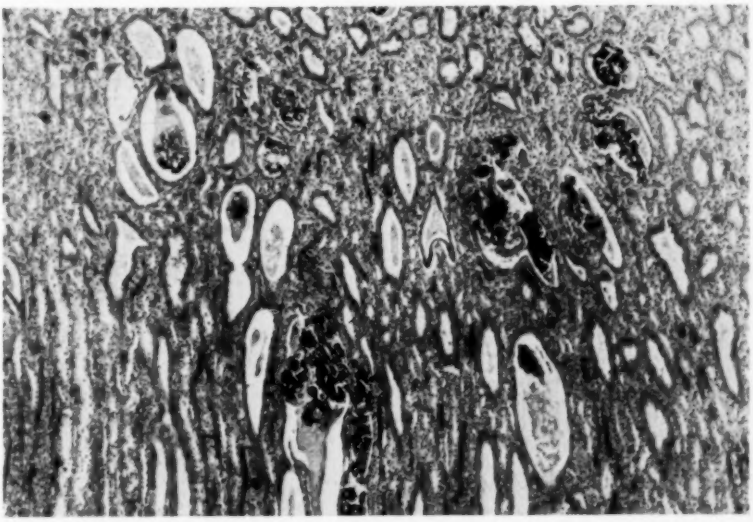


Fig. 15.—Photomicrograph (medium power)—kidney. Deposits in the collecting tubules with resultant dilatation of these tubules.

The microscopic appearance of the other organs including the osseous system, bone marrow, and brain were within normal limits.

GENETIC ANALYSIS

In the pedigree obtained from the parents, no other individual was found with a condition resembling this syndrome (see Chart I). The maternal grandmother of the patients (II, 9) is 68 years of age and is diabetic. The maternal grandfather died of a heart attack at the age of 67 years. A maternal aunt (III, 6) had a child who died of hydrocephalus. The paternal grandmother (III, 4) is 60 years of age and is in good health. She had one miscarriage and lost one child who died of tuberculosis (IV, 5). The whereabouts of the paternal grandfather is unknown.

Following the appearance of the second child a further search of the literature was of no avail. Correspondence with other centers resulted in photographs of two infants with somewhat similar appearances to ours.[2, 3] In one photograph in particular[2] the resemblance to our cases was striking. In neither of these, unfortunately, was there any identifying data available for the infant shown in the photograph.

It would appear, therefore, that we are dealing with an exceedingly rare condition. The repetition in the one family suggests the operation of genetic factors. Since both parents are normal, there arises the possibility of a dominant mutant gene. However, since there are two affected individuals one would have to consider cluster mutations, that is, the same type of mutation occurring at least twice in the germ cells of one of the parents. This seems highly improbable. A more plausible explanation is that the syndrome is determined by a single rare recessive gene that arose as a mutation in a common ancestor and was carried through the intervening generations before coming to light as the result of a consanguineous union.

DISCUSSION

From an academic standpoint it is unfortunate that more detailed laboratory and metabolic studies were not undertaken on these infants. Practically, it was decided that as little could be done for these children and as their hold on life seemed so tenuous, extensive investigations were not feasible or justified.

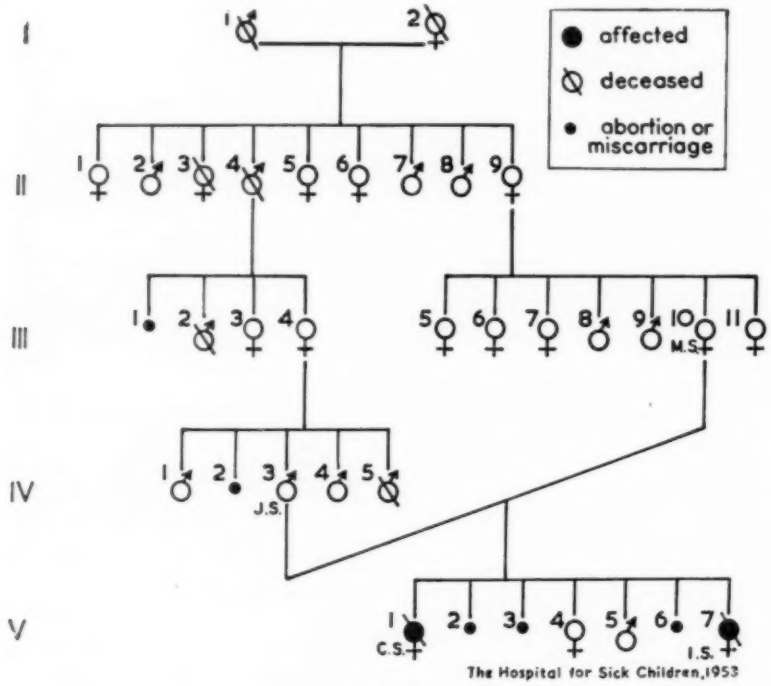


Chart I.

It seems probable that these infants represent the homozygous combination of rare recessive genes which has resulted in widespread somatic abnormalities. In the light of our

present knowledge and available information it is impossible to sort out the various factors involved and their interrelationship.

The salient features which would indicate that this is a hitherto unreported syndrome are as follows:

(a) Apparent cessation of growth on or about the seventh month of pregnancy. Both infants at the time of death were approximately the development and weight of a seven-month fetus. Dystrophy, muscle wasting, and emaciation were prominent features.

(b) The most outstanding stigma characterizing the syndrome, and the one which suggested the term "leprechaunism" was the peculiar and unusual facies. The large wide-set eyes, big low-set ears, Negroid features, and hirsutism gave to these infants an elfin or gnomelike appearance.

(c) Profound endocrine disturbances were indicated by the histologic changes in the ovaries, pancreas, breast, hypertrophy of the clitoris and possibly the thymus and pituitary. Follicular cysts are not infrequently found in infants of 2 months, but the total mass of the ovaries is never as great as it was in these infants. It is also unlikely that the changes in the breasts present at the time of death were persistence of neonatal hyperplasia. Hyperfunction of the islet tissue of the pancreas, suggested by histology, was supported by bioassay of the pancreas which demonstrated greatly increased amounts of insulin. The hypertrophy of the clitoris is also evidence of abnormal hormonal stimulation. The mechanism for this change is apparently not the same as seen in the adrenogenital syndrome. The hypertrophy was not of the same magnitude and the adrenals were histologically normal.

(d) The severe emaciation suggested metabolic aberrations. This was supported by the microscopic changes in liver. The abnormal deposits of glycogen and iron in the liver were most unusual. The hypertrophy and calcinosis of the kidneys might be related to metabolic and/or endocrine dysfunction.

(e) The development of subcutaneous abscesses in each infant could have been merely part of the general debility. On the other hand, it might have been an indication of a special susceptibility to infection.

SUMMARY

1. A clinical and pathological syndrome is described to which the term "leprechaunism" has been applied.

2. The syndrome is probably the homozygous combination of a rare recessive gene, the homozygous combination being facilitated by the consanguinity of the parents.

We wish to thank Dr. H. E. Edwards, senior staff physician of The Hospital for Sick Children, for permission to use the clinical records and for his kindness in arranging interviews with the parents.

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COLORED STRIAE IN ADOLESCENT CHILDREN

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STRIAE, both colored and white, have been frequently observed in obese subjects, during pregnancy, in connection with Cushing's syndrome, and other conditions, and more recently in patients treated with cortisone or ACTH. They have commonly been considered as sequelae to periods of rapid growth and particularly to the rapid deposition of adipose tissue with subsequent injury to the elastic fibers of the skin. In usual medical parlance they are loosely called stretch marks and are designated as *striae cutis distensae*. They have not ordinarily been considered to have any physiological significance.

The purpose of this discussion is to call attention to striae in general, and more specifically to the colored striae that occur in adolescent children who may or may not have fat pads. We suggest that the pink striae found frequently in both fat and thin boys and girls in the adolescent period may represent an adrenocortical stimulation and might be described as a physiological Cushing's syndrome.

Our interest in striae was aroused a few years ago during a study of a group of adolescent children which entailed somatotyping and complete examinations in the nude. During the physical examinations of these children and in their somatotype photographs, striae were frequently observed. (It may not be generally realized that in most of our school examinations and, in fact, in studies on growth and development, children are not always completely undressed, and consequently striae are not noted.) Our interest in striae was particularly aroused when a 13-year-old boy, whom we had previously examined, appeared with his mother with the intention of seeking advice from a "skin specialist." This boy, who was large and obese, had been skiing and suffered a fracture which required his hospitalization. After three weeks in bed, he noticed violaceous-colored lines that completely encircled his thighs and involved the gluteal regions. The patient's nurse and family thought that these lines were caused by wrinkles in the sheets. They were the red, almost hemorrhagic, striae typical of an obese adolescent.

In the literature, although reference is made frequently to the white striae which often occur in such conditions as pregnancy, Cushing's syndrome, etc., attention is seldom called to colored striae, or to their association with growth and development. The following references to red striae, however, have been found.

The curator of Guy's Hospital[1] in 1861 described some new wax models showing striae in a girl of 13 years that resembled the lineae gravidarum. These lines were first red, then turned purple, and finally became white. Although the striae were noted in a 13-year-old girl, there was no mention of an association with puberty.

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Weber Parkes,[2] under various titles, has described striae in adolescents who were thin. He suggested that these so-called *idiopathic striae atrophicae* were due "to a temporary basophilic hyperpituitarism at and following puberty" and were not due to stretching of the skin. Later Weber Parkes[3] suggested that these striae might be associated with adrenocortical hyperplasia.

Weill and Bernfeld[4] recently have reviewed "the problem of striae." Although they published no data, they believe that all striae show the same histological picture, and by the same token, the striae in pregnancy, in acute infections, in nutritional disturbances, in Cushing's syndrome, and in puberty are all due to the same cause, namely, to a hyperactivity of the adrenal cortex. These authors state that of girls between the thirteenth and fourteenth years, 15 per cent had pink or white striae, and that 17-ketosteroids and 11-oxysteroids were increased. They suggest that the striae are not due to rapid growth and may be observed in thin persons. They consider that "the steroid activity in these adolescents is associated with excessive catabolism of the protein of the skin that results in the appearance of striae."

Striae in young patients have been noted after treatment with cortisone. Sprague and co-workers[5] observed striae in a 17-year-old boy with rheumatic fever, but these may have been present before the treatment. Striae were seen by these authors in five additional patients and were regarded as different from ordinary striae because of their purplish color.

Wilkins and associates[6] have made similar observations of striae after treatment with cortisone in cases of pseudohermaphrodism. In two cases "conspicuous reddish striae in parallel longitudinal lines over the buttocks and in the trochanteric regions" developed. These authors considered the "rapid deposition of fat in these regions" the cause of the striae and suggested that they were "similar to that which occurs in normal females during adolescence." It is interesting that these striae are said to have disappeared after the cortisone was omitted.

Macrae-Gibson[7] has recently reported a group of ninety-two patients with pleural effusion and red striae. These were institutional patients, and there is no statement indicating that striae were not present before hospitalization. Striae were noted in 41.8 per cent of all patients in this group and in 70 per cent of those between 16 and 17 years. Steroid studies showed similar values in a group of patients with striae and in a control group. The author believes that an increase in body weight was the probable cause of the striae, but states that cortical adrenal activity cannot be excluded as a factor.

Since reference in the literature to colored striae in adolescent children is so limited, it seemed of interest to us to determine the incidence of striae in this growth period and find, if possible, the relation of striae to the established developmental signs of adolescence.

A study was therefore undertaken of 190 healthy, adolescent children between the ages of 10 and 16, most of whom were patients of the Orthodontic Clinic of the Forsyth Dental Infirmary for Children in Boston, while others were seen in private practice for routine school examinations. This

study has been in progress for four years, and most of the patients have been observed periodically.

The age of the children in this study was partly determined by the age of the patients visiting the Orthodontic Clinic, namely from 10 to 16 years. Therefore, the observations of striae in this study were mainly confined to that age group, although it can be stated from personal observations that striae rarely occur before 9 years of age, but may be seen after 16 years of age, especially in boys.

Complete physical examinations were made of each patient, together with x-rays of the wrists for bone age, somatotype photographs, and weight and height determinations. Special attention was paid to the presence of colored striae, to the presence of acne, to the stage of development of breasts in girls and of genitals in boys, and to pubic and axillary hair in both sexes. The following criteria for assaying the stage of development of breasts, pubic and axillary hair, and genitals were used:

Pubic Hair

Stage 0. Absent.
Stage 1. Sparse, pigmented, straight or only slightly curled.
Stage 2. Moderate amount, pigmented, curled and spread.
Stage 3. Has assumed the traditional inverted triangle form, pigmented, and tightly curled.

Axillary Hair

Stage 0. Absent.
Stage 1. Present, but scanty.
Stage 2. Present in a moderate amount.
Stage 3. Present, abundant, covering the region of the axilla.

Breasts

Stage 0. Undeveloped.
Stage 1. Bud stage—of areola, papilla with very slight mammary gland enlargement.
Stage 2. Areola and papilla form a secondary mound above the level of the breast with some mammary gland enlargement.
Stage 3. Papilla projects, areola no longer elevated, definite mammary gland enlargement.

Genitals

Stage 0. Undeveloped.
Stage 1. Slight enlargement of testicles, no lengthening of penis, no pigmentation.
Stage 2. Moderate enlargement of testicles and some lengthening of penis, slight pigmentation.
Stage 3. Marked enlargement and lengthening and definite pigmentation.

Of the 190 children under study, sixty-seven (or 35.3 per cent of the series) showed striae. This group of sixty-seven with positive striae consisted of nineteen boys (or 28.4 per cent of the boys) and forty-eight girls (or 71.6 per cent of the girls). There was considerable sex variation in the group with striae. In the group without striae there were sixty-three boys and sixty girls. As will be noted in Table I, the highest incidence of striae in girls occurred between the twelfth and fourteenth years, and the highest incidence in boys was from 12 to 15 years. Striae were noted, however, in all the age groups studied in boys and girls.

TABLE I. AGES AT WHICH STRIAE WERE FIRST OBSERVED

AGE (YEARS)	MALES	FEMALES	TOTAL
9-10	0	0	0
10-11	3	4	7
11-12	2	7	9
12-13	4	15	19
13-14	4	9	13
14-15	4	8	12
15-16	2	5	7
Total	19	48	67

The appearance of these striae is similar to that noted in pregnancy and in Cushing's syndrome. As seen in Fig. 1, they, in general, form a pattern with parallel lines, with a tendency to be circinate and with considerable variation in design. The lesions vary greatly in intensity and many times could be easily overlooked, while in other cases they may cover the gluteal region and almost suggest the lash marks of a whip.

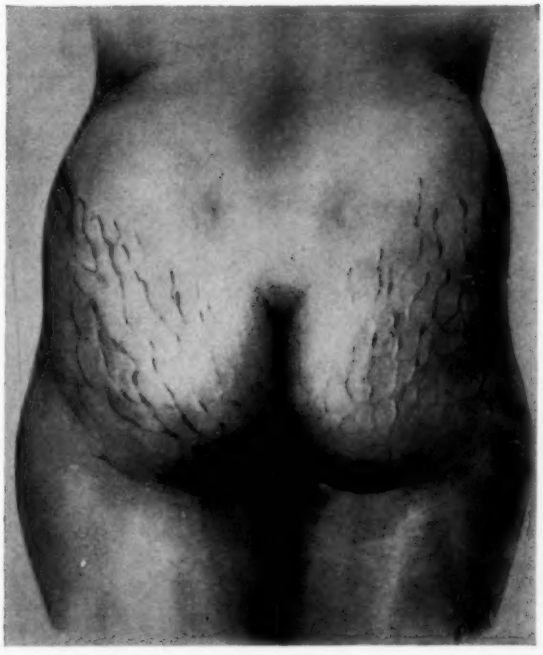

Fig. 1.—Typical striae in a girl of 15 years (from a drawing).

When striae first appear, they are pink to violaceous in color with an almost hemorrhagic appearance; they may remain in this stage for many months or years. The pink, purplish color gradually fades, and white lines, somewhat smaller than the original striae, finally develop. The colored striae which occur over the crest of the ilium are the last to retain their color. The length of striae is difficult to determine, as striae frequently join others after a few centimeters; the same is true of their width, which may in some subjects initially be 2 to 3 mm. and later attain a width of about 1 cm. The color of striae over the gluteal region is somewhat more extreme when the patient is erect and cannot be completely blanched by pressure. In general, the color and design of the striae are noted bilaterally. Most of the colored striae, especially as seen in the early stages, are slightly elevated to the touch of the finger. The late stages of striae may easily be overlooked, although if the skin of the affected area is made taut,

the white meshwork of striae can readily be detected.

The change in color of striae may be illustrated by the following case histories.

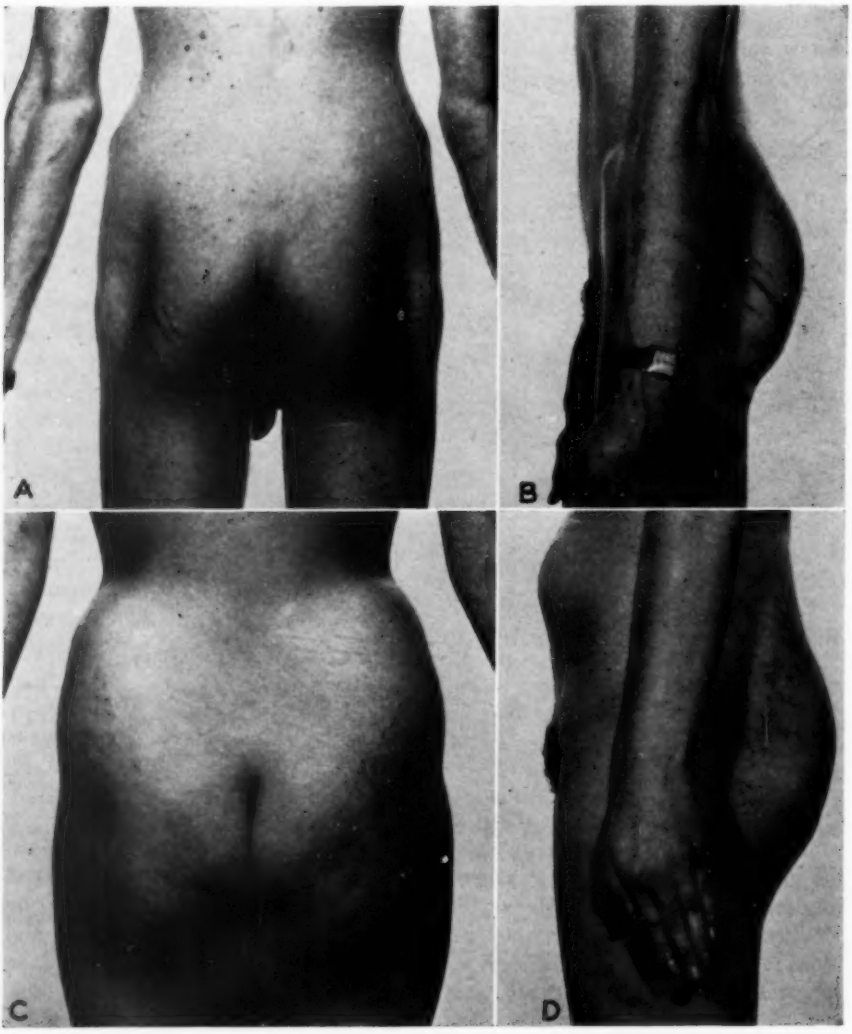

Fig. 2.—*A* and *B*, Striae in a thin boy, aged 17 years, 2 months. *C* and *D*, Striae in a moderately obese girl, aged 14½ years.

CASE 7.—J. A. When this girl was first seen, she had pink to red striae at 12 years 5 months of age. They were located on the thighs bilaterally over an area below the anterior superior spine of the ilium. She was last seen at 13 years 10 months, and the striae were mostly white with a few pink lines still present.

CASE 182.—P. K. Pink striae were noted over the gluteal region in this girl at 11½ years of age. One year

later, pink and white striae were noted on the breasts, gluteal region, and over the inner aspects of the thighs. When the patient was seen again at 14 years, all striae were white, and she showed adult developmental characteristics.

teal area were pink, while in the posterior gluteal region there were many white striae. At 16 years a few colored striae remained but there was an extensive meshwork of white striae involving most of the gluteal region.

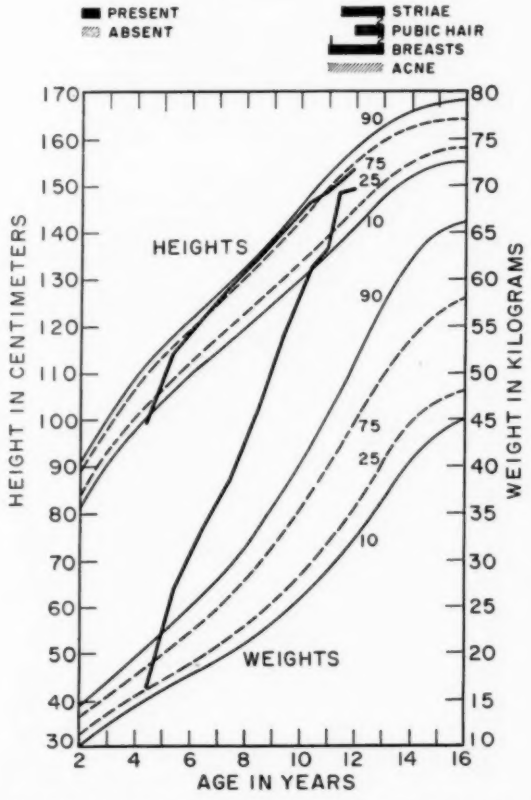

Fig. 3.—Height and weight chart of obese girl showing relation of striae to stages of development.

CASE 11.—B. B. Colored striae were first noted bilaterally over the gluteal region in this 11-year-4-month-old, thin girl. She was seen again at 12 years, and the striae were white.

CASE 179.—W. J. This boy had been under medical observation since birth. At 14½ years of age pink striae were first noted over the entire gluteal region bilaterally. At 15 years 1 month the striae in the superior glu-

The striae are located most frequently over the upper thighs. They are occasionally seen over the breasts in girls, and in one instance were noted over the lower abdomen. The most common site is the gluteal region as shown in Fig. 2.

The striae are seen starting at the level of the crest of the ilium and

running diagonally over the trochanteric region to the posterior gluteal. At times they may completely encircle the upper thighs and may appear above the knees over the inner aspects of the thighs. There is a tendency for the striae to be distributed symmetrically on both sides.

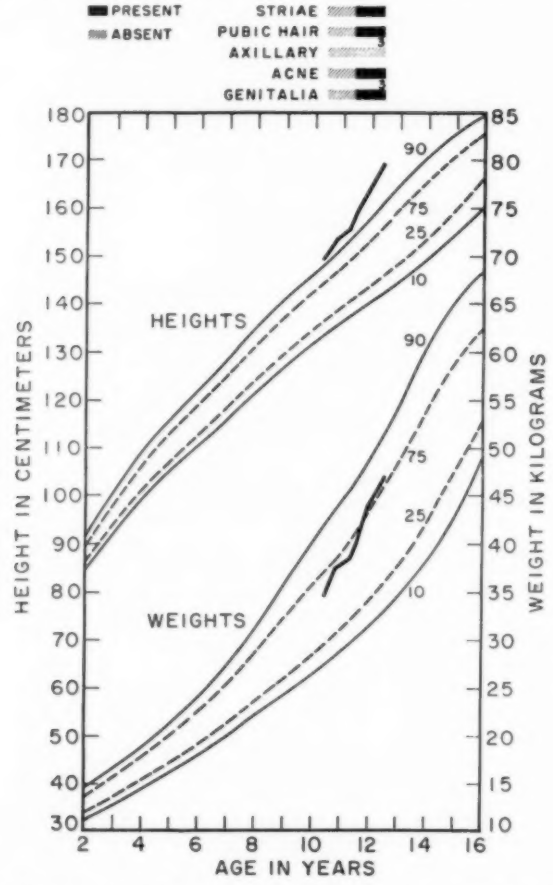

Fig. 4.—Height and weight chart of thin boy showing relation of striae to stages of development.

They vary greatly in the extent of their distribution and in their pattern. Often a few elevated pink vertical striae will be seen near the anterior superior spine, and in the more extreme cases all the gluteal region will be involved. At times the wavy, interrupted pink lines will be almost horizontal to the axis of the body. The striae on the breasts may involve all quadrants or portions of the mammae. They radiate outward from the areola as wavy pink lines about 1 to 2 cm. apart. These may occur before or after the gluteal striae.

Striae, either colored or white, are generally associated with excess deposits of subcutaneous adipose tissue.

In the group of 190 children who were observed consecutively, obesity was noted in forty-eight. Of these, thirty, or 62.5 per cent, showed typical colored striae. The striae occurred most frequently in obese girls and over 66.6 per cent of this group exhibited striae. There were only sixteen obese boys in the series and eight of these exhibited striae. In spite of the association of striae with obesity, it was not uncommon to find colored striae in children, especially boys, who showed little or no subcutaneous fat. Typical weight charts of an obese girl with striae, a thin boy with striae, and a thin girl with striae will be found in Figs. 3, 4, and 5.

The results of the comparison of striae with other physical changes associated with adolescence are shown in Table II, in which the stages of adolescent development and the incidence of striae, acne, and menarche are recorded in reference to sex and age for six consecutive years. The highest incidence of striae appears to occur in girls in the 12- to 13-year period, in which there is increasing frequency of the third stage of development of hair and breasts, while in boys, striae were noted more frequently between the ages of 13 and 15 years. However, striae may appear between the ages of 9 and 10 in girls with no axillary hair and prior to menarche

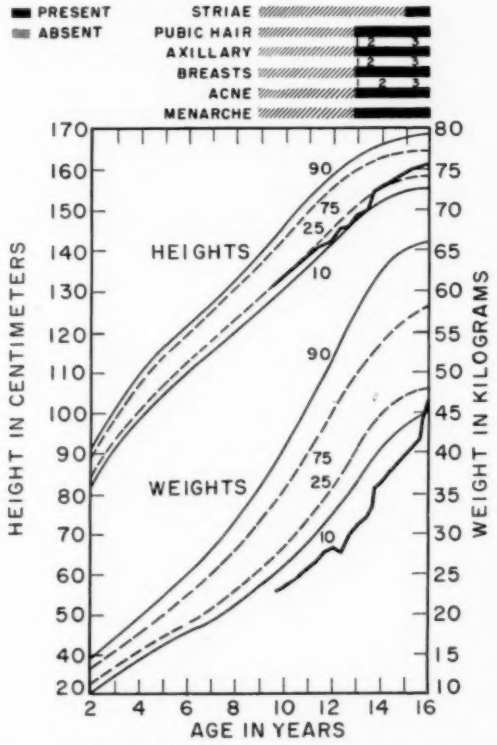

Fig. 5.—Height and weight chart of thin girl showing relation of striae to stages of development.

and in boys with no pubic or axillary hair and with no visible development of the genitals. Table II shows that striae were seen at all ages between 10 and 16 years and were more commonly seen after the menarche in girls and at a later age in boys.

Acne was a frequent finding in this group of adolescent children. This condition was somewhat arbitrarily defined as clinical acne if it was disfiguring and suggested mild stages of so-called acne vulgaris. Cases were described as mild when an efflorescence of the face was discernible but caused no disfigurement in the estimation of the observer. In the group of sixty-seven children with colored striae there were thirty-two or 47.7 per cent with well-defined acne, while in the group of 123 children with no striae only eleven children or 8.9 per cent had comparable acne. Acne was not only more frequently seen in the striae group but was distinctly more severe and more resistant to ordinary measures of treatment. In a number of children with severe acne, improvement took place as the initial pink striae finally changed to the terminal white lines.

As colored striae were so commonly found in the age group between 10 and 16 years, it seemed of interest to know whether they occurred at earlier or later ages. Although no systematic study has been made, our observation of hundreds of children under 10 years indicates that striae seldom occur in normal children during the first five years. They are not seen in extremely obese babies, nor in obese children under 6 years.

However, striae were noted in some children at 9 years of age, and even

TABLE II. SHOWING ASSOCIATION OF DEVELOPMENTAL STAGES WITH COLORED STRIAE IN SIXTY-FIVE CHILDREN

	AGE (YEARS)											
	10-11		11-12		12-13		13-14		14-15		15-16	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
No. of Cases	3	4	2	7	4	15	4	8	4	7	2	5
Pubic Hair												
Stage 0	1	1	1	1	0	0	0	0	0	0	0	0
Stage 1	2	2	1	1	3	2	1	0	1	1	0	0
Stage 2	0	1	0	3	0	3	0	2	0	0	1	0
Stage 3	0	0	0	2	1	10	3	6	3	6	1	5
Axillary Hair												
Stage 0	3	2	2	1	3	4	2	0	1	0	0	0
Stage 1	0	2	0	4	0	2	1	2	0	2	1	0
Stage 2	0	0	0	1	1	2	0	0	0	0	0	0
Stage 3	0	0	0	1	0	7	1	6	3	5	1	5
Genitals in Boys and Breasts in Girls												
Stage 0	1	0	0	0	0	0	0	0	0	0	0	0
Stage 1	2	4	2	0	3	1	1	0	1	0	0	0
Stage 2	0	0	0	5	0	5	0	0	0	1	1	0
Stage 3	0	0	0	2	1	9	3	8	3	6	1	5
Acne												
Present	0	1	0	5	2	7	3	3	3	3	2	3
Absent	3	3	2	2	2	8	1	5	1	4	0	2
Menarche												
Present		0		4		8		8		7		5
Absent		4		3		7		0		0		0

earlier in a few instances, as shown by the following case histories:

The first case is the record of N. H., a child 6 years 11 months of age, who was seen with typical purplish striae under the trochanteric regions and under the inner aspects of the thighs. This girl was definitely obese and had a slightly elevated blood pressure (110/70). The only sign of external sexual development was the presence of pubic hair in the first stage and a slight enlargement of the external genitals. This is the youngest child that we have observed with striae.

Another child, R. B., 7 years 8 months of age, was obese and showed pink striae in the trochanteric regions and under the inner aspects of the thighs. This boy showed no external sexual development and presented no symptoms. His blood pressure also was fairly elevated at 110/60. This child was seen six months after the striae were first noted, and they were now replaced by a meshwork of white striae.

A third child, C. C., a girl who had been under medical observation since birth, was seen at 9 years of age, and no striae were noted; but at 9 years 10 months, extensive pink striae were seen over her gluteal region. This child, like the others, was definitely obese and had a slightly elevated blood pressure. She presented no symptoms, and like the other two children, showed normal behavior and normal scholastic progress. In this instance, the only other sign of adolescence was somewhat enlarged external genitals.

DISCUSSION

This study has called attention to the occurrence of pink striae in the period of development designated as adolescence. There seems to be no doubt that striae are associated with steroid activity. They apparently occur not infrequently as one of the earliest signs of puberty before other well-recognized criteria are evident. It would seem likely that they may occur quite independently of axillary hair and almost simultaneously with pubic hair and external genital development. The common association of acne and colored striae again emphasizes their probable relationship to adolescence. As in acne, we have no definite explanation for the presence of striae in some children and not in others. It may be associated with the collagen content of the skin in various parts of the body in different individuals.

Although we as yet have no steroid assays in these children with striae, it seems likely that the stimulus for their development may be present for varying periods. In other words, striae occur spontaneously for short periods simulating the administration of cortisone or they may last for years during the complete period of puberty.

It is of interest to speculate whether there are other factors than adrenocortical stimulation that are responsible for the formation of striae. The mechanical theory has been the commonly accepted one, and it is generally believed that excessive deposition of adipose tissue, especially if this occurs relatively suddenly, is the fundamental cause for the pink striae. One cannot state at this time that obesity may not influence the formation of striae, but one can state with certainty that striae not infrequently occur in children who clinically may be thin or have no excess subcutaneous fatty tissue. Although colored striae are most commonly associated with obese adolescent girls, obesity itself is not a sine qua non factor. Besides the mechanical effect of the sudden deposition of adipose tissue in the formation of colored striae, normal cleavages in the

skin pattern and tension of the skin from physical activities may be regarded as possible predisposing factors.

The exact incidence of striae in the adolescent period cannot be determined by this study but must be based on a longitudinal observation of children at frequent intervals during their entire adolescence. Although it was found that about 25 per cent of the girls and 10 per cent of the boys showed pink striae, it seems probable that the incidence is much higher. From routine examinations of children of 9 to 16 years, striae are now looked upon as a very common finding. Striae in their various stages of development have previously been overlooked because observers have hesitated to examine the adolescent in the nude. Furthermore, the patients themselves had rarely noticed their own striae.

SUMMARY

During a study on aspects of growth and development of children between the ages of 10 and 16 years, pink to violaceous-colored striae over the gluteal region were commonly noted. It was observed that these striae may occur at any stage of adolescence but were more frequent in the later period. They were always associated with one or more of the recognized signs of adrenocortical stimulation. There was a definite association with acne, genital and breast development, pubic hair, and the menarche.

Of interest were the changes that took place in these colored striae, which gradually became white, leaving a permanent white meshwork of lines. While the colored striae were very commonly found in obese subjects, especially girls, many adolescent children who had striae were not obese. Conversely, it was not unusual to see a truly obese child in a stage of adolescence without striae.

Our observations indicate that:

1. Colored striae are a definite sign of adoleseence.
2. Striae become white during the later stages of adolescence.
3. Striae are not necessarily associated with obesity and are not to be considered merely as "stretch marks."
4. Acne is more common and more severe in adolescent children with colored striae.

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SUSCEPTIBILITY OF RECENTLY ISOLATED STRAINS OF HEMOPHILUS INFLUENZAE TO ELEVEN ANTIBIOTICS IN VITRO

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IN A previous report from this laboratory, Finland and Wilcox[1] presented the results of in vitro tests for sensitivity of a number of strains of *Hemophilus influenzae* isolated in 1949 or earlier to seven antibiotics, namely, penicillin, streptomycin, bacitracin, polymyxin D, polymyxin B (Aerosporin), chlortetracycline (Aureomycin), and chloramphenicol (Chloromycetin). There was a remarkable similarity in the range of concentrations of six of these antibiotics required to inhibit the majority of the strains; only bacitracin among these antibiotics was found to be essentially inactive. Since that time there have been several reports of similar studies[2-8] involving varying numbers of strains tested primarily with chloramphenicol, penicillin, streptomycin, chlortetracycline, and oxytetracycline (Terramycin), and some tested for susceptibility to sulfonamides[5, 6] and to polymyxin D.[4] The results of most of these studies were summarized by Zinneman[8] and in an editorial comment[9] accompanying his paper and that of Franklin and Garrod.[7] Those studies essentially confirmed the similarity of the action of the antibiotics studied on the majority of the strains tested; the sulfonamides showed a greater variation in activity against different strains and a large proportion of strains were more resistant to them. Smooth encapsulated strains, which could be classified serologically, were similar in their susceptibility to the noncapsulated strains.[8] Resistance could easily be increased in vitro to penicillin and to streptomycin, and such increased resistance of *H. influenzae* was observed in one clinic in strains from three of eight patients treated with the latter antibiotic alone[5]; increased resistance to chloramphenicol was said to develop more slowly.[5]

The present study was undertaken as part of a re-evaluation of the status of the available antibiotics against common bacterial infections in view of the widespread use of many of these agents in recent years. In particular, it was of interest to determine (1) the susceptibility of the common pathogenic bacteria to the antibiotics that were recently introduced and (2) whether there has been any significant change in the resistance of these organisms to the antibiotics that have already been in wide use for several years. This report deals with recently isolated strains of *H. influenzae* and their susceptibility to eleven antibiotics, including six that had been included in the earlier study made in this laboratory with strains of this species.[1]

MATERIALS AND METHODS

The strains used in the present study were obtained from routine

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

*Aided by a grant from the U. S. Public Health Service.

cultures submitted for bacteriological examination between November, 1953, and June, 1954. A few of the strains were obtained from the Children's Medical Center through the courtesy of Dr. Harry Shwachman; the rest were isolated and identified at this hospital by Miss Marion E. Lamb and Miss A. Kathleen Daly of the bacteriological laboratory of the Mallory Institute of Pathology. The sources of the strains are listed in Table I. The proportion of serologically typed strains was smaller than in the earlier series[1]; all of the strains obtained from blood or cerebrospinal fluid were smooth and encapsulated and identified serologically, while none of the others, including those obtained from purulent exudates, could be "typed." Most of the strains (about 80 per cent) were from sputum or throat cultures of patients with acute respiratory infections or acute exacerbations of chronic bronchopulmonary infections.

TABLE I. SOURCES OF STRAINS OF HEMOPHILUS INFLUENZAE ISOLATED NOVEMBER, 1953, TO JUNE, 1954

SOURCE	NUMBER OF STRAINS
Sputum (79) or throat (2)	81
Cerebrospinal fluid	7 (all type B)
Blood	5 (4 type B, 1 type C)
Eye	4
Ear	3
Wound (human bite)	1
Urine	1
Total	102

The following antibiotics were used: potassium penicillin (1 unit considered equal to 0.6 μg) and streptomycin sulfate obtained commercially, chlortetracycline (Aureomycin), tetracycline (Achromycin), oxytetracycline (Terramycin), carbomycin (Magnamycin), chloramphenicol (Chloromycetin), polymyxin B sulfate (Aerosporin), erythromycin (Ilotycin), bacitracin (51.7 units per mg.) and neomycin sulfate.*

Tests for antibiotic sensitivity were carried out in the same manner as in the earlier study. Serial twofold dilutions of the antibiotics were incorporated into heated horse blood ("chocolate") agar and several strains were streaked on the surface of each series of plates. The inoculum was prepared by scraping a large loopful of the surface growth of a freshly grown culture and thoroughly emulsifying it into 1 ml. of broth; a 2 mm. loopful of the suspension was then streaked onto a segment of each of the antibiotic-containing plates. The streaked plates were incubated at 37° C. and examined for growth with the aid of an engraver's lens (3x). The susceptibility of a strain was defined as the minimum concentration of antibiotic, in micrograms per milliliter, on which there was no discernible growth after incubation for forty-eight hours.

RESULTS

The results of all the tests made with the recently isolated strains are summarized graphically in Fig. 1. In this figure the susceptibility of all the strains tested with each antibiotic is represented in a single, cumulative,

*Aureomycin and Achromycin supplied by Lederle Laboratories through the courtesy of Dr. Stanton M. Hardy; Terramycin and Magnamycin furnished by Chas. Pfizer & Co., Inc., through the kindness of Dr. Gladys L. Hobby; Chloromycetin provided by Dr. E. A. Sharp of Parke, Davis & Co., Aerosporin provided by Dr. Donald F. Searle of Burroughs Wellcome & Co.; Ilotycin furnished by Dr. R. S. Griffith of Eli Lilly & Co., bacitracin provided by Dr. H. J. Byrne of Commercial Solvents Corporation, and neomycin sulfate supplied by Dr. H. F. Hallman of The Upjohn Co.

percentage-distribution curve. The steepness of all of the curves indicates the relatively uniform susceptibility of the different strains to each antibiotic. It is also seen here, as in the previous study,[1] that the curves representing most of the antibiotics fall fairly close to each other, indicating a close similarity in the susceptibility of the strains to most of the antibiotics that were studied. In the present study, as in the earlier one, serologically "typed" strains and those which could not be typed were similar in their sensitivity to each of the antibiotics.

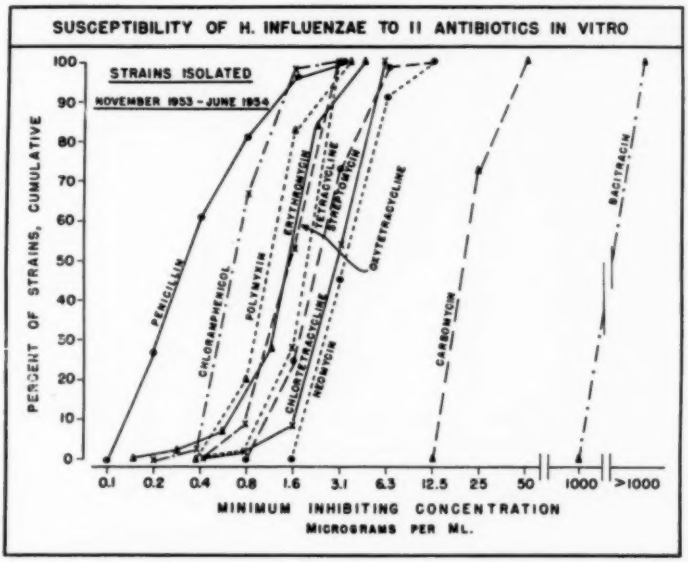

Fig. 1.

Of all the agents tested, penicillin appears to be the most active, on a weight basis, and chloramphenicol ranks next, followed by polymyxin. The remaining antibiotics, except carbomycin and bacitracin, are about equally active; carbomycin, however, is appreciably less active than all the others except bacitracin, the latter being essentially inactive, all strains surviving exposure to 1,000 μg (equivalent to 51.7 units) per ml. Of the three tetracycline analogues, chlortetracycline appears to be slightly less active than the other two, but this may be due to the instability of the chlortetracycline during the forty-eight hours of incubation used in these tests.

A comparison of these results with those obtained in earlier studies in this laboratory[1, 10] is shown in Table II. On the whole, there appeared to be no striking or significant difference between the susceptibility of the strains recently isolated and those studied in 1949 or earlier with respect to the antibiotics that were used in both studies. Likewise, the susceptibility to erythromycin of strains isolated in 1952[10] and of those tested

with this antibiotic in the present study was very similar.

However, slight differences, which suggest minor increases in resistance of the recent strains to chlortetracycline, chloramphenicol, and polymyxin B, and a slightly greater susceptibility of the recent strains to penicillin, can be noted in Table II; these may be the result of minor differences in the materials and techniques used in the different studies and may be considered as falling within the limits of error of the method used. In the case of bacitracin, the lot used in the present study was more active (51.7 units per mg.) than the one used earlier (34 units per mg.), and this may account for the observed difference, although that is relatively unimportant. However, the possibility that some of the observed differences indicate gradual trends cannot be entirely ruled out from these data. In particular, the greater resistance of the recent strains to streptomycin and the fact that none of these strains were inhibited by less than 1.6 μg per milliliter of this antibiotic, whereas 27 per cent of the earlier ones were inhibited by concentrations of 0.2 to 0.8 μg per milliliter, may reflect a real change, although still a minor one.

The occurrence of strains of *H. influenzae* of high resistance to any antibiotic, comparable to the appearance of staphylococci markedly resistant to penicillin, streptomycin and the tetracyclines,[11] has not been observed in this study. However, the appearance of strains of *H. influenzae* with markedly increased resistance to streptomycin during the course of treatment with this agent has previously been noted in this clinic[12] as in others,[5, 13] but was not observed in the present study.

TABLE II. IN VITRO SUSCEPTIBILITY OF RECENTLY ISOLATED STRAINS OF HEMOPHILUS INFLUENZAE TO ANTIBIOTICS: COMPARISON WITH RESULTS PREVIOUSLY REPORTED FROM THIS LABORATORY

ANTIBIOTIC	YEAR	NUMBER OF STRAINS	MINIMUM INHIBITING CONCENTRATION, μG PER ML.								
			0.2	0.4	0.8	1.6	3.1	6.3	12.5	25	50
			Per cent of Strains								
Penicillin	1949*	30	10	13	30	30	13	0	4		
	1954	90	27	34	20	16	3				
Streptomycin	1949	60	2	8	17	33	33	5	2		
	1954	90				24	49	26	1		
Chlortetracycline	1949	30			47	47	6				
	1954	90			2	5	47	46			
Oxytetracycline	1954	90			9	44	47				
Tetracycline	1954	90			2	26	72				
Chloramphenicol	1949	16			100						
	1954	90		1	66	31	2				
Polymyxin B	1949	16		6	44	50					
	1954	11			18	55	27				
Erythromycin	1952†	18		5	28	50	17				
	1954	90		1	5	21	57	16			
Neomycin	1954	11					46	46	9		
Carbomycin	1954	11								73	27
Bacitracin	1949	17	All inhibited by 750-3,000 μg per ml.‡								
	1954	90	All resistant to 1,000 μg per ml.								

*Finland and Wilcox.[1] Some of these strains were isolated before 1949.
†Haight and Finland.[10]
‡7 (24%), 13 (41%), and 6 (35%) inhibited by 750, 1,500 and 3,000 μg per ml., respectively.

DISCUSSION

The results of the tests for susceptibility of recently isolated strains of *H. influenzae* to the currently available antibiotics confirm the earlier findings in showing the similarity of the in vitro action of most of the antibiotics against all strains, both the type-specific ones and those which could not be classified serologically. Among the antibiotics not included in the earlier study, oxytetracycline and tetracycline appear to be somewhat less active than chloramphenicol but more active than chlortetracycline, the poorer showing of the latter probably being due to its relative instability under the conditions of the test. Erythromycin, when tested in 1952 against strains of *H. influenzae* isolated at that time, appeared to be quite active;[10] this was confirmed in the present study, its activity being similar to that of oxytetracycline. Only a small number of strains were tested with neomycin and carbomycin; the former appeared to be about as active as chlortetracycline whereas the latter was appreciably less active than any of the antibiotics studied, except bacitracin.

When compared with the results of the earlier studies, the data show an apparent increase, though very slight, in resistance to each of the antibiotics that were tested on both occasions, except in the case of penicillin, against which the recently isolated strains appear to be slightly more sensitive. The differences in most instances are slight and are probably not significant; they may possibly be the result of differences in the materials and techniques used in spite of attempts to keep them uniform. Nevertheless, there was an appreciable proportion of strains among those studied in 1949 that were sensitive to low concentrations of some antibiotics which either failed to inhibit any of the recent strains or which were effective against only a much smaller proportion of the strains; this was particularly true with respect to streptomycin. No strains of unusually high resistance to any of the antibiotics, other than bacitracin, were observed in the recent series. This would suggest that the antibiotic susceptibility of *H. influenzae* has, in general, not shared the fate of the staphylococcus in this respect. The possibility cannot be excluded, however, that a significant proportion of the strains of *H. influenzae* that are most susceptible to some antibiotics are gradually being eliminated as a result of their widespread use; this, obviously, was not the case with penicillin, the most widely used of all the antibiotics.

Mention has already been made of the appearance of strains of *H. influenzae* highly resistant to streptomycin in patients during the course of treatment with this antibiotic for infections in which only sensitive strains are recognized before the treatment was started; such resistant strains usually appear early in the course of treatment. This has not been reflected in the findings reported here, although it is possible that resistant strains are to be found in the community, but were not encountered in the small sample of strains studied. On the other hand, the failure to uncover such strains may be due to other factors; for example, the resistant strains may lose their resistance when the streptomycin is

withdrawn, or they do not survive in competition with the normal flora, or they have properties which militate against their causing disease or spreading from person to person.

The data reported are concerned with the relative susceptibility of strains of *H. influenzae* to antibiotics in vitro. The interpretation of these data in terms of the relative effectiveness and usefulness of these agents against human infections with such organisms can only be assessed on the basis of actual clinical use, but adequate data concerning such use are not available for most of these agents. There are, however, considerations apart from the in vitro susceptibility of the strains, and even of their effectiveness in individual cases or small groups of cases, on the basis of which one can predicate the relative clinical usefulness of these agents. Penicillin, though it is the most active in vitro on a weight basis, is much less effective clinically because of the very high dosage required to sustain the bactericidal levels in the blood and tissues and because of its poor penetration into the cerebrospinal fluid. Chloramphenicol is the most active in relation to the concentrations attainable in blood and cerebrospinal fluid and is preferred by many workers on that account; however, in spite of its relative effectiveness[7, 8] its use in chronic respiratory infections associated with *H. influenzae* has been abandoned by some workers because of the occasional occurrence of severe and even fatal blood dyscrasis attributable to such use.[7]

Chlortetracycline has also proved effective in *H. influenzae* infections, including meningitis[3, 4] in spite of its poor penetration into the cerebrospinal fluid, and the same is probably true of oxytetracycline which yields even poorer concentrations in spinal fluid. From this point of view, tetracycline, because of the relatively higher serum and cerebrospinal fluid levels it yields, coupled with its lower gastrointestinal toxicity, would appear to be more useful than its two analogues; this has been confirmed in a preliminary manner in a small number of cases recently observed at this hospital.

Polymyxin B, though highly active in vitro, is too toxic for sustained systemic use in the dosage that is probably required for most infections with *H. influenzae;* in some circumstances, however, the use of this agent in proper dosage systemically for short periods or in small amounts intrathecally, intraventricularly, or topically in other localized infections may sometimes be very useful and even lifesaving. The same may also be said of neomycin, which is much less active in vitro. Data concerning the use of erythromycin in *H. influenzae* infections are lacking; this agent also penetrates poorly into the cerebrospinal fluid. Carbomycin, because of its low activity in vitro and the low concentrations attainable in body fluids, is probably of no value in these infections and the same may be expected to be true of bacitracin which is practically inactive in vitro.

SUMMARY AND CONCLUSIONS

Strains of *Hemophilus influenzae* isolated between November, 1953, and June, 1954, were tested for susceptibility to eleven antibiotics in vitro. On a weight basis, penicillin was the most active and chloramphenicol

ranked next. Except for carbomycin and bacitracin, the remaining antibiotics (streptomycin, polymyxin B, the three tetracycline analogues, erythromycin, and neomycin) were all nearly equal in their activity and only slightly less active than chloramphenicol. Chlortetracycline was slightly less active in vitro than oxytetracycline or tetracycline, but this was considered to be due to the instability of chlortetracycline under the conditions of the test. Carbomycin was considerably less active than any of the others except bacitracin, which was essentially inactive. The clinical interpretation of these in vitro findings was discussed.

The results obtained with the recent strains were, on the whole, similar to those obtained with some of the same antibiotics in previous years; however, a smaller proportion of the recent strains were susceptible to the lower concentrations of each of these antibiotics except penicillin. Strains highly resistant to any of the antibiotics except bacitracin were not encountered. Although the differences noted are probably not significant, the possibility must be considered that these findings indicate a gradual elimination of strains of *H. influenzae* that are most sensitive to some of the antibiotics, other than penicillin, that have been widely used.

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ACUTE FAMILIAL INFANTILE HEREDODEGENERATIVE DISORDER OF THE CENTRAL NERVOUS SYSTEM

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THE heredodegenerative diseases of the central nervous system present marked variations in symptomatology as well as pathology which are difficult to classify. As a result, many combinations of the different syndromes exist. Nevertheless, the group is clinically characterized by certain findings—normal examination at birth, insidious onset of illness, progression of symptoms, and a family history of a similar nervous disorder.

However, there are only few known heredodegenerative disorders which give rise to marked symptomatology in early infancy, affecting the mentality as well as the general neuromuscular development. These are the diffuse degenerative sclerosis of Krabbe and Pelizaeus-Merzbacher, the cerebral gray matter degeneration described by Alpers, and amaurotic family idiocy. Bielschowsky[13] considered Krabbe's the acute form, Scholz's the subacute form, and Pelizaeus-Merzbacher the chronic form of the same disease process. He differentiated these three types of cerebral sclerosis from Schilder's disease by the latter occurring in older patients with a gradual onset and absence of family history. Familial cases of Schilder's disease have been described, but the clinical features of these cases resemble Pelizaeus-Merzbacher disease.

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Krabbe's disease was first described in 1913, and approximately fifty cases have been reported in the literature.[1-4, 6, 8, 9, 21] The pathological picture is characterized by extensive involvement of the white matter of the brain, whereas the gray matter is intact. Histologically, there is evidence of demyelinization and gliosis. The myelin sheaths are destroyed, and glial tissue makes its appearance in an attempt to repair the damaged areas. Kaijaar and Lundquist[9] reported a case in which the lipid content of the white matter of the central nervous system was determined chemically and found to be diminished. This finding is in agreement with the decreased myelinization seen histologically.

Jervis[3] found, in his two cases, glia elements with large nuclei which he considered embryonic in character rather than reactive. He postulated that this disease is due to a primary affection of the glia and consequent impairment of the normal metabolism of myelin.

The clinical picture of Krabbe's disease is usually ushered in by repeated convulsions occurring in an apparently previously normal infant, 4 to 6 months of age. These convulsions may be preceded by fever and irritability and are followed by a rapid downhill course. As the condition progresses, there occurs muscular hypertonicity, episodes of tonic and clonic convulsions, and finally flaccid

paralysis. Impaired vision progresses to blindness, hyperacusis is replaced by deafness. The infant may vomit excessively, and gains poorly. His entire physical development is impaired. He loses skills previously exercised, such as holding his head up, rolling over, reaching for objects, or following objects. He no longer smiles or responds to animated faces. His existence becomes vegetative, and his activities are greatly diminished. The apathy is progressive without remissions. Finally death occurs within a year or two. No effective treatment is known.

Alpers[22] reported a group of cases where fairly uniform degenerative lesions were found in the cerebral gray matter. Onset of symptoms was noted from 4 months to 5 years of age. Convulsions were usually an early symptom. These were followed by progressive rigidity of the entire musculature, by mental deterioration, and athetoid movements. If speech was ever acquired, it was soon lost. Eventually the patient became blind, deaf, and demented.

Our paper concerns three male siblings, each of whom developed a clinial picture similar to Krabbe's and Alpers' cases.

There is no consanguinity or neurological disorders in the family. Both parents are Rh positive. The mother's first pregnancy terminated unsuccessfully after five months of gestation.

CASE REPORTS

CASE 1.—A. N., a male infant, was born Sept. 26, 1942 (mother's second pregnancy), a precipitous delivery after a twenty-four-hour labor. The mother noted that he was always "very quiet." At 4 months of age he suddenly began to have many generalized and focal convulsions.

He was hospitalized at the Coney Island Hospital, from January 27 to March 5, 1943, where the following findings were noted. Eyes did not follow light; nystagmoid movements of eyes were present; strabismus was present. Funduscopic examination revealed marked pallor of the discs, which was believed to be due to optic atrophy. The child appeared not to hear. The anterior fontanel was flat. There was no nuchal rigidity. Abdominal and cremasteric reflexes were absent. Deep tendon reflexes increased, especially on left side. There were occasional twitchings of lips, eyelids, and extremities.

The laboratory findings including spinal fluid examination were nonrevealing. X-ray studies of skull, long bones, and chest revealed no abnormal findings. The child was transferred to Kings County Hospital for further study. Pneumoencephalogram revealed: "Asymmetry in position of the ventricular system with displacement of both ventricles slightly to the right of the midline, localized atrophy of the right frontal region with considerable widening of the subarachnoid space. Findings consistent with an atrophic lesion in the right frontal hemisphere. He was diagnosed as having a birth injury of the brain."

He continued having convulsions after his discharge from the Kings County Hospital and was rehospitalized subsequently on several occasions at the Coney Island Hospital. During his second admission Dec. 7 to 12, 1943, at 14 months of age, it was noted that his developmental behavior showed a marked lag in that he did not sit up, walk, or talk. He had frequent episodes of crying.

Third admission to Coney Island Hospital was Dec. 31, 1943, to Feb. 4, 1944. At 15 months of age he showed no essential change in symptomatology.

His fourth and last admission to Coney Island Hospital one month

later followed an episode of afebrile convulsions, with no essential change in neurological findings other than further deterioration. There were physical signs of a left lower lobe pneumonia, which was confirmed by x-ray of the chest.

He continued to have generalized twitchings of the entire body, with rigid extension of the right lower extremity. He was transferred to Kings County Hospital March 7, 1944, where he died one week later at 17 months of age. The cause of death was stated to be mental deficiency due to birth injury and cerebral spastic infantile paralysis. No autopsy was performed.

CASE 2.—G. J. N., the second sibling, was delivered May 28, 1946, normal spontaneous delivery, after a three-hour uncomplicated labor. The birth weight was 8 pounds.

Aug. 16, 1946, at almost 3 months of age, this child was admitted to the Maimonides Hospital. One day prior to admission, his mother noted sudden jerky spastic movements of the upper extremities, fibrillary twitchings of the tongue, and "stiffness" of his entire body. The child was afebrile. Examination revealed a well-developed child, weighing 12 pounds 11 ounces. Physical examination was normal. Neurological examination showed only fibrillary twitching of tongue. Pupils reacted to light. Deep and superficial reflexes were intact. Fontanel was not bulging. Optic fundi were normal. Laboratory findings including blood chemistry, urine, blood smear, spinal fluid, x-ray studies of long bones, skull, and chest were all within normal limits.

On admission it was noted that the infant's eyes moved about constantly while he was awake. Twelve hours after admission he had a generalized convulsion which lasted ten minutes. Convulsive seizures continued during his hospital stay despite anticonvulsant medication. At times he would suddenly let out a high-pitched sharp cry.

Since convulsions persisted, he was transferred Oct. 20, 1946, to the New York Hospital for further neurological work-up. A pneumoencephalogram revealed definite cerebral atrophy on the right side, but was thought to be bilateral since there was no shift of the dilated lateral and third ventricles. Ophthalmological examination revealed optic atrophy, total blindness, but no other changes. The child was discharged as unimproved on Nov. 8, 1946. The diagnosis was "congenital cerebral dysgenesis of undetermined origin."

At 15 months of age (July 30, 1947) he was admitted to the Coney Island Hospital because of convulsions, fever, and vomiting. The examination revealed head drawn back, pupils dilated and fixed, neck rigid, legs drawn up, knees flexed. Kernig and Brudzinski signs were positive. Deep reflexes were not elicited in the lower extremities. Heart rate was rapid, and lung findings revealed moist râles throughout both lung fields.

Blood count, spinal fluid including cell count, protein and sugar content were normal. X-ray studies of skull and chest were negative throughout the stay in the hospital. Convulsive seizures recurred and were uncontrolled by anti-convulsants. He died Aug. 25, 1947.

Post-Mortem Examination.—

Brain: There was marked edema of entire surface. Vessels were moderately injected. Cerebrum, cerebellum, and medulla exhibited no other pathology externally. Brain after fixation: There was marked subarachnoid edema. On serial sections there was moderate dilatation of the lateral ventricles and third and fourth ventricles. Choroid plexus average. This was only slight encroachment of the dilated ventricles on parenchyma of most of the brain. There was apparent normal demarcation between gray and white matter. The nuclei of the base of the brain and cerebellum were pale and poorly demarcated.

Microscopic:

Brain: Meningeal vessels were engorged. Intrinsic vessels were similarly congested and showed edema of perivascular lymph spaces.

Cerebellum: There were moderate edema and loss of cell clarity. Sections from motor area and basal nuclei showed edema and granular changes in cell cytoplasm.

Anatomical diagnosis: Birth defect of brain. Motor cell degeneration, unknown etiology with convulsive seizures.

Post-mortem examination was performed at Coney Island Hospital by Dr. Harold Fink.

Restudy of a small section of the brain by Dr. Stanley Aronson yielded the following report. "Myelin, axonal phosphotungstic acid hematoxylin, and Nissl body studies revealed no parenchymal degeneration consistent with Krabbe's disease. Within the sparse fragment of paraffinated tissue there was full myelination. Of some interest may be the extensive degree of lipochrome cytoplasmic degeneration noted in the cortical neurons of the submitted specimen. This was not associated with any cellular diminution or interstitial reaction. Similarly there was no axonal deficit noted."

A few of the smaller parenchymal venous channels were the sites of fibrin occlusion, but this change is considered nonspecific and often associated with terminal marantic states in pediatric diseases.

CASE 3.—R. N.

First Admission.—

Present Illness: R. N., a 4½-month-old infant, was admitted to the Maimonides Hospital on Sept. 11, 1950, with a history of a three-day fever (101° to 10° F.) and intermittent twitchings of the right side of mouth and right eyelid for twelve hours. He was treated intensively with antibiotics for a "red throat" prior to admission.

Past History: He was born April 26, 1950, weight 8 pounds 3 ounces. Pregnancy and delivery were normal. The child thrived and developed normally. At 2 months the child smiled, followed objects, and recognized his parents. He held his head up at 3 months, and was making an effort to sit up at the time of the onset of the present illness. He was well up to the onset of the present illness. He was given the first injection of diphtheria, pertussis, and tetanus two weeks prior to onset of his present condition. Other than "crankiness" he had no untoward effect from the inoculation.

Physical Examination: The temperature was 102.8° F. There was twitching of the right side of the face and the eyelids on the right. The head was deviated to the right and the eyes to the same side. The lower extremities were held in tonic spasm. Each convulsive seizure was accompanied by a shrill cry. Neurological findings at this time were negative, including eye-ground examination. The rest of the physical examination was nonrevealing.

Laboratory Findings: Complete spinal fluid examination, blood count, urine, blood chemistry, Wassermann reaction, agglutination reactions, typhoid, paratyphoid, protein and brucella revealed normal findings.

Course and Treatment: Sedation with phenobarbital for convulsive seizures. Child was treated with antibiotics; temperature was normal after three days. During his twelve-day stay in the hospital twitchings recurred, unaccompanied by fever. The child uttered loud, shrill, piercing cries from time to time as evidence of cerebral irritability. X-ray films of skull revealed no abnormalities. Mantoux test was negative.

The infant was readmitted on Oct. 18, 1950, for fever and convulsions, at first limited to the right side and later becoming generalized and clonic in nature.

Neurological examination (P. J. K.) revealed child apathetic, paying no attention to the examiner, and showing no interest in his surroundings.

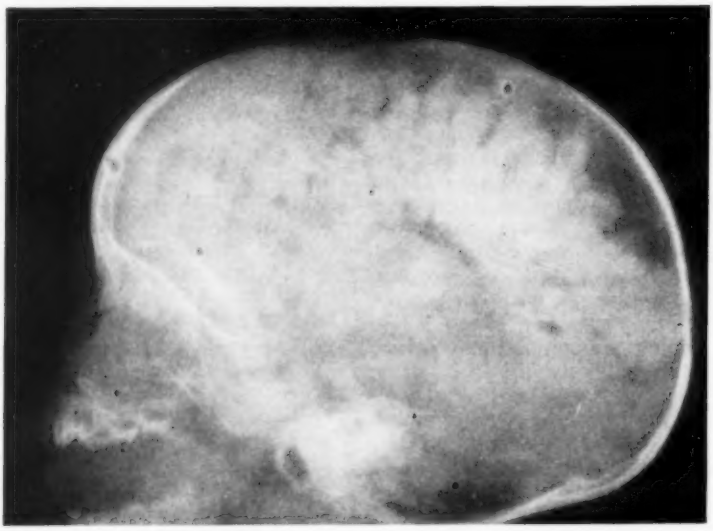

Fig. 1.—Pneumoencephalogram revealing cortical atrophy of the left parietal and occipital areas.

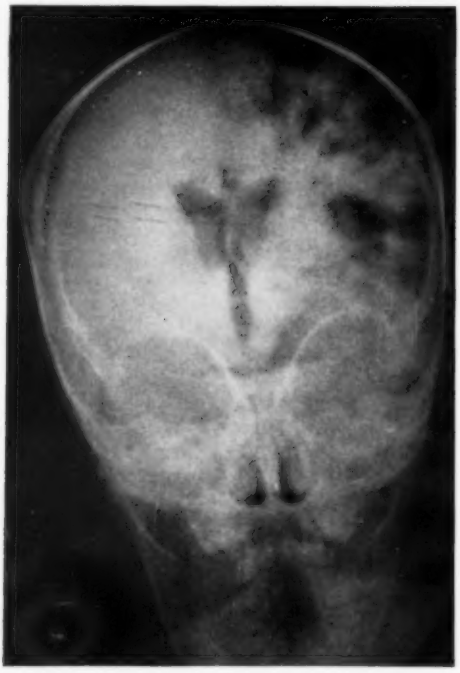

Fig. 2.—Pneumoencephalogram showing a large rarefied area suggesting porencephaly with cortical atrophy of the left parietal and occipital areas.

He did not follow or catch objects in his gaze. There was no head control. Tone of lower extremities was increased, deep tendon reflexes exaggerated. Pupils reacted sluggishly to light. There was internal strabismus with nystagmoid movements. Vision was impaired. He blinked when loud noises were made at either ear. Magnus de Kleijn sign was absent. Eye grounds were normal. The remainder of the neurological examination was nonrevealing.

Laboratory findings including examination of spinal fluid, repeated urine examinations, blood counts, blood sugar, protein, BUN, calcium, phosphorus, sodium potassium, alkaline phosphatase, CO_2 were all within normal limits.

X-ray studies of skull and long bones were normal. On Nov. 3, 1950, pneumoencephalography was performed. The films revealed marked cortical atrophy on the left side, involving the parietal and occipital lobes. There was a large rarefied area posteriorly suggesting porencephaly. The lateral and third ventricles were somewhat larger than average. No air was visualized on the right side. This was interpreted as lack of drainage, but not ruling out atrophy on the right side.

On Nov. 8, 1950, eye consultation revealed negative findings except for lack of coordination of the eye globes.

Electroencephalography was performed by Dr. Louis Greenstein. The findings were indicative of organic brain disease with epileptogenic tendency in the right frontal area.

On Dec. 2, 1950, the child was discharged to the pediatric outpatient department for follow-up. At that time his convulsions were fairly well controlled by phenobarbital ¼ grain t.i.d. However, on follow-up the child developed a clonic type of convulsive seizures unaccompanied by fever and uninfluenced by any type of sedative or other medications. The child died in June, 1953, at 3 years of age, having had repeated respiratory infections.

Autopsy permission was refused.

COMMENT

The cases reported are clinically indistinguishable from Krabbe's disease and also resemble Alpers' cases. The electroencephalogram and the pneumoencephalogram indicate diffuse organic brain disease. The one autopsy obtained and analyzed by two pathologists independently revealed cortical motor cell degeneration. It also showed extensive cortical lipochrome degeneration, a finding not ordinarily seen in these cases. No involvement of the axis cylinders or myelin sheaths were found.

Apparently the brain may undergo degeneration in a number of ways, leading to variations in clinical syndromes.

Table I gives the main points of difference between the degenerative disorders under consideration.

Other conditions to be considered in the differential diagnosis are kernicterus, toxoplasmosis, infantile tetany, subdural hematoma, congenital cerebral defects, and birth injuries.

Convulsions are fairly common in infancy, and in approximately 18 to 20 per cent of cases that occur between 1 and 6 months of age, the cause is unknown.

A familial incidence involving two or more siblings has been noted in most of the acute heredodegenerative disorders. Consanguinity has been noted in some cases. It has been postulated that in many of these disorders sex-linked recessive traits are present in an overt form only in males and are transmitted directly only by females.[10]

In view of the familial nature of the disease, the parents have been

TABLE I. FAMILIAL DEGENERATIVE DIFFUSE SCLEROSIS

TYPE	ONSET	CLINICAL COURSE	SYMPTOMS (PROGRESSIVE)	PATHOLOGY (HISTOLOGICAL FEATURES) (DEMYELINIZATION AND GLIOSIS)
1. Krabbe (acute infantile form)	Before 1 yr. of age. Usually at 4 to 6 mo. of age	Rapid, lasting several months to a year	1. Convulsions 2. Muscular hypertonicity 3. Tonic and clonic convulsion 4. Blindness and deafness 5. Mental degeneration 6. Flaccid paralysis	1. Axis cylinder severely involved 2. Immature forms of glia frequently encountered
2. Scholz (subacute juvenile transitional form)	3 to 10 yr. of age	Lasts several years	1. Cortical deafness 2. Cortical blindness 3. Spastic paralysis 4. Tremors 5. Athetosis 6. Dementia 7. Epileptic attacks	The fatty products of degeneration (prelipids show peculiarities of solubility and staining)
3. Pelizaues-Merzbacher (chronic infantile form)	Early infancy e.q., 3 mo. of age	Lasts for years into adulthood	1. Rotary head movement and nystagmus 2. Spasticity of legs with increased deep tendon reflexes 3. Cerebellar ataxia (scanning speech, intention tremors) 4. Dementia 5. Involuntary movements 6. Paralysis contractures, deformities	Perivascular island of myelin are preserved in characteristic manner
4. Alpers' disease (degeneration of cerebral gray matter)	First few months of life to 5 yr. of age	Death occurs in early childhood. No family history	1. Defective development from early infancy 2. Convulsions in childhood. Progressive rigidity 3. Dementia	Loss of cells in cortex and basal ganglia. Myelin destruction
5. Amaurotic family idiocy	2 to 8 mo. of age	Death occurs between second and third year	1. Visual disturbance 2. Cherry-red spot in retina 3. Sluggishness 4. Loss of previously acquired motor skill	Ganglion cells throughout the entire central nervous system show swelling due to deposit of lipoid droplets with the nuclei displaced to the periphery of the cells

warned about the prognosis of future progeny.

SUMMARY

An acute heredodegenerative disorder of the central nervous system affecting three successive siblings is described. A characteristic picture, clinically indistinguishable from Krabbe's disease and resembling Alpers' disease, is repeated in all three infants. This condition occurred in siblings in early infancy and ran a rapidly fatal course. It was characterized by convulsions,

mental degeneration, and finally paralysis. The pathological findings in the only case autopsied showed cortical changes and no evidence of demyelinization. Variations exist in the way the brain undergoes degeneration and it is not always possible to place them in a definite classification. It is important to warn the parents of the prognosis of future progeny.

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TREATMENT OF ERYTHROBLASTOSIS FETALIS BY EXCHANGE TRANSFUSION

Statistical Analysis of Results

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AT THE present time, exchange transfusion is generally accepted as the most satisfactory treatment of erythroblastosis fetalis. During the past few years minor modifications in technique have been introduced, which have served to improve the outlook in this disease, as evidenced by a further reduction in the mortality rate and in the frequency of neurological sequelae. This, therefore, seems to be an opportune time to review our experiences with exchange transfusion in erythroblastosis.

While there is some difference of opinion regarding the rationale of exchange transfusion, there is unanimity concerning its efficiency and effectiveness. We should like first to review briefly our own concept of how the treatment brings about its salutary effect. For simplicity, the discussion is limited to typical cases of **Rh_0** sensitization, although the same principles apply in cases of A-B-O hemolytic disease, and isosensitization to Hr, Kell, and other blood factors.

RATIONALE OF EXCHANGE TRANSFUSION

During the pregnancy, univalent **Rh_0** antibodies produced by the Rh-negative sensitized mother pass through the placenta into the fetal circulation and combine with the fetal Rh-positive cells.[1, 2, 3] There is no good evidence that the Rh agglutinogen exists in cells other than the red blood cells or in any of the body fluids or secretions.[4] In consequence, once all of the combining sites on the baby's red blood cells have united with the antibody, the excess accumulates free in the baby's plasma and body fluids until, if the pregnancy lasts long enough, the antibody titers in the maternal and fetal plasma become equal. The height of the titer of the maternal Rh antibodies, which in turn determines the degree of coating of the fetal Rh-positive red cells, is the principal factor governing the severity of the disease in the infant.[5, 6] Mere coating of the fetal cells by antibodies appears to be innocuous, since such cells can circulate and function like normal cells. To produce a pathological effect such as clumping or lysis, it is believed[7] that some accessory factor, complement-like in nature, must also be present. In general, the fetus is protected while in utero against the harmful effects of the antibodies, probably because complement and related substances are incompletely developed before birth. However, if the maternal antibody titer is high and has been present for a sufficient time before birth, the baby may be stillborn, or, if

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born alive, may exhibit severe manifestations of the disease.* In many instances the baby appears normal at birth, but manifestations of the disease become evident in the early neonatal period.

Reports in the literature that stillbirths can be averted by treating the sensitized Rh-negative mother during pregnancy have not been confirmed. Treatment with so-called Rh hapten, diethylenesulfonate, progesterone, exchange transfusion on the mother, "desensitizing" injections of Rh-positive blood, and cortisone have all proved to be useless.[8] Preparations of so-called Rh hapten were found to be inactive both in vivo and in vitro.[9] Exchange transfusion on the mother, an expensive and elaborate procedure, produces only a transient lowering of antibody titer, and then only if very large amounts of blood are used,[10] while injections of Rh-positive blood serve only to increase the degree of sensitization. Recent reports[11] claiming beneficial effects from ACTH and cortisone therapy used during pregnancy, and also for the treatment of the affected infant, could not be confirmed by us[12] or other investigators.[13]

When the baby is born alive the physician is presented with the choice of treating the baby expectantly, or of giving small transfusions of whole blood or packed cells as anemia develops and recurs, or of performing an exchange transfusion, immediately. About a decade ago there was some debate as to whether the blood used for transfusion should be Rh positive or Rh negative.[14, 15] In the milder cases it appeared to make little difference which type was used, so long as enough blood was given to counteract the anemia. In the more severe cases it was soon found, however, that when Rh-positive blood was used many more transfusions had to be given, in some instances as many as ten or more.[16] This is readily understandable since in the severe cases, where the maternal antibody titer is high, not only are the baby's cells maximally coated with antibody,[17] but there is a large excess of antibody in the infant's plasma ready to combine with any fresh Rh-positive cells introduced into the circulation. In fact, in occasional instances where the father or some other Rh-positive donor was used, frank hemolytic reactions resulted.[15] On the other hand, when Rh-negative donors were used, the hemolytic process ceased as soon as all of the baby's own cells had been destroyed and replaced by donor's cells.[18] This suggested that the baby's recovery could be accelerated by removing the baby's blood and replacing it with Rh-negative blood at birth, instead of waiting for the baby's cells to be hemolyzed.[19]

At first the main argument advanced in favor of exchange transfusion was that it was more efficient in that it shortened the period of morbidity for the baby, and it was considered that simple transfusions were equally effective in lowering the mortality rate provided the baby was not allowed to die from anemia. It was soon realized that anemia was not the only cause of death in erythroblastosis, and was in fact an infrequent one. Many babies who had been treated adequately by simple blood transfusions, and some who had never developed any significant anemia, and, therefore, were never transfused, rap-

*This corresponds with observations made in vitro that when the antibody titer is high, less complement is needed to bring about hemolysis.

idly became more and more deeply jaundiced and died on the second to fifth day of life with pathological evidence of nuclear jaundice (kernicterus), frequently together with liver necrosis and intrapulmonary hemorrhage. This led some workers[20, 21] to suggest that the Rh antigen might be present in the tissues of the Rh-positive baby, and that the pathological effect might be an expression of the union of antibody with tissue antigen in the brain, liver, and lungs. However, as has been pointed out already, valid experimental evidence for the presence of Rh antigen outside of the red cells has never been presented. Furthermore, in instances where the mother's whole blood, which is the original source of antibodies, was used for transfusion, hepatic and cerebral damage generally did not occur.[22, 23] We feel, therefore, that it is not the free antibody which is the immediate noxious agent, but the baby's coated red cells.

Since there is no direct relationship between the depth of the jaundice and the degree of anemia, it is evident that the jaundice in this disease is not solely hemolytic in origin. Moreover, though brain damage is more likely to occur in severely jaundiced babies, some severely jaundiced babies may recover completely, while others with lighter jaundice may die with brain damage. We believe, therefore, that the tissue damage is due primarily to vascular injury resulting from intravascular conglutination of the baby's coated cells.[7] Damage to the liver results in jaundice, while blockage of the circulation in the brain not only produces nuclear damage, but also allows bilirubin to cross the blood-brain barrier and stain the dead and dying ganglion cells. If this concept is correct, obviously tissue damage cannot be prevented or counteracted by the simple addition of blood. But if the coated Rh-positive cells are removed before intravascular clumping occurs, and these are replaced by Rh-negative cells which are incapable of combining with the free Rh antibody, tissue damage can be prevented.[24] This then is our concept of the rationale of exchange transfusion.

At birth, except in the most severely affected infants, any tissue damage which may be present appears to be reversible. That kernicterus is rarely, if ever, found in the newborn or stillborn infant may be attributed to the fact that fetal bilirubin formed in utero passes into the maternal circulation and is thus largely excreted. That many babies, apparently normal at birth, rapidly develop jaundice and evidence of organic injury may perhaps be due to the increase in the concentration of complement or conglutinin in the infant's circulation during the early neonatal period, with resulting hemolysis or intravascular clumping.[7, 25] Thus, if the baby's coated red cells are replaced by compatible Rh-negative cells as soon after birth as possible this eventuality can be averted.

TECHNIQUE OF EXCHANGE TRANSFUSION

Theoretical Considerations.—Theoretically, replacement of the baby's red cells should be complete, but since bleeding and administration of blood must be carried out simultaneously this ideal can never be attained. For convenience, a pint of blood or about twice the baby's blood volume is used, and this is sufficient to accomplish an 85 per cent replacement, which is adequate in the average case.

The degree of replacement can be calculated with the aid of a formula derived by Wiener and Wexler,[24] which is as follows: $100(1 - e^{-v})$ where v represents the volume of blood used for the exchange expressed in units of the baby's blood volume. For example, assuming a blood volume of 250 ml. for the average infant, withdrawing and administering 500 ml. of blood will produce an exchange of about 86 per cent. Strictly, the formula is valid only for continuous exchange transfusions such as are carried out by the radial artery-saphenous vein method. Formulas have been derived which are applicable to intermittent exchange transfusion,[25] such as is used with the umbilical catheter method in which syringefuls of blood are alternately injected and withdrawn. Actually, the simpler formula of Wiener and Wexler can be used for such transfusions as well, since the estimated values are substantially the same.

The formula of Wiener and Wexler fails to take into account the fact that it is the replacement of red blood cells rather than of whole blood that is important, since the chief purpose of the procedure is to remove the baby's coated red cells. Veall and Mollison[27] and Wallerstein and Brodie[28] have therefore derived formulas in which the hematocrits of the baby's and donor's blood are also taken into account. A similar formula has been derived by Wiener and Wexler.[29] Obviously, the more anemic the baby is initially, the more efficient the exchange transfusion will be for any given volume of blood exchanged. On the other hand, such babies are likely to have a high erythroblast count, and "autotransfusion" of new red cells from the marrow would in such cases tend to nullify partially the effect of the exchange transfusion.

In our very first exchange transfusion we used whole citrated blood.[30] Such blood, because of dilution with citrate solution, had a low hematocrit, so that if equal volumes were administered and withdrawn the baby would be left anemic at the termination of the procedure. Therefore, our practice was to inject 50 ml. of blood in excess of the amount withdrawn. When a number of babies died despite what appeared to be adequate therapy, we attributed this to the fact that a substantial quantity of the baby's coated cells remained in the infant's circulation. This led us to increase the volume of blood exchanged to 1,000 ml., given either at one time, or on successive days in quantities of 500 ml. of citrated blood each day.[31, 32] Again to allow for the dilution with citrate we increased the amount injected over that withdrawn by 100 ml. When deaths occurred with this procedure as well, we considered the possibility of overloading being a contributing cause. In the next modification attempted, therefore, the blood was concentrated by centrifugation, and packed cells (hematocrit 0.75) were used for the exchange.[29] With this modification the high hematocrit of the injected blood limited the amount of blood that could be given and withdrawn to 150 ml., lest the baby be made too polycythemic. The procedure was thus rendered shorter, but at the same time less effective, as was proved by the fact that a few babies with neurological sequelae appeared in this series. A compromise procedure was finally adopted, in which only part of the citrated plasma was

removed and the total volume given reduced to about 400 ml. (hematocrit (0.50), with no excess of blood given over that withdrawn.[33] In very severely affected babies, moreover, we resumed the practice of doing a second exchange transfusion when indicated.

Initially it was our practice to inject about 50 ml. of blood first and then start the withdrawal of blood, maintaining the margin until the end of the procedure. However, other investigators[28, 34] showed that the efficiency of the exchange could be increased by first bleeding and later starting the infusion. When subsequent experience demonstrated that the infants tolerated the diminished blood volume quite well, we also adopted the practice of bleeding the baby at the outset, even when it exhibited anemia. For the past three years, therefore, during which period we have used only concentrated blood for our exchange transfusions, we start the procedure by first withdrawing 50 ml. of blood. As the withdrawal is continued, injection of blood is started at a rate which makes good the deficit early in the procedure, so that at the termination the amounts administered and withdrawn are equal.

Technique.—The following is a detailed description of the procedure as we now perform it.

The infant is immobilized on a circumcision board by the use of flannel wrappings, leaving one arm and one leg free. The leg is strapped down with adhesive tape, and the saphenous vein exposed at the ankle through a transverse incision made anterior and superior to the medial malleolus. The vein is cannulated with a blunt 20 gauge needle (a 20 gauge polyethylene catheter may also be used), which is tied in place. Two hundred units of heparin diluted in 2 ml. of saline are injected through the needle, and a three-way stopcock is attached, which in turn bears the tubing from the blood reservoir and a 10 ml. Luer-Lok syringe for the injection of the blood. Before any injection of blood is made, the radial artery is isolated through a transverse incision on the radial side of the wrist just proximal to the head of the radius. The artery can be recognized as a moderate-sized, plump vessel whose appearance and size are not unlike those of the saphenous vein at the ankle. There are no veins in this part of the forearm with which it may be confused. The artery is cleaned carefully, lifted up on a closed mosquito clamp, and nicked by placing the point of a scalpel at about the midpoint and making an angled incision through the flattened wall. The flow of blood is immediate and copious. The blood may be collected conveniently in 30 ml. medicine glasses, which in turn are emptied into a larger graduated receptacle for final measurement. Before any blood is administered at the ankle, 50 ml. of the infant's blood is permitted to run out through the arterial incision. Injection of blood is then commenced at a rate which keeps pace with the arterial flow and which makes up the deficit by the time that the 90 ml. mark is reached. Equal quantities of blood are administered and withdrawn (about 400 ml.), which in the average infant will effectuate an exchange of about 90 per cent. During the procedure, calcium gluconate is administered intravenously in quantities of 1 ml. of a 10 per cent solution for every 100 ml. of concentrated blood given. At the termination of the transfusion, the incisions are closed with fine silk sutures and pressure bandages applied. Neither the artery nor the vein is ligated, and it may be assumed that they recannulate in the process of healing. Postoperatively, the infants are given 100,000 units of penicillin every eight hours for two days, and, if necessary, are placed in an incubator and given continuous oxygen therapy. Feedings are routine. In instances

where the procedure is repeated, the opposite arm and leg are generally used, but an attempt may be made to recannulate the vein (but not the artery) used for the first transfusion.

It will be noted that a small amount of heparin is introduced at the beginning of the procedure in order to facilitate the bleeding. Actually, the procedure can be carried out without heparin, but the small amount used is innocuous, and its effect is nullified by the termination of the transfusion. We have never encountered any harmful effect that could be attributed to this quantity of heparin. The rate at which the procedure is carried out is of considerable importance. The more protracted it is, the less likely is it to cause any reaction, but for convenience we attempt to complete the procedure in about forty-five minutes, but not in less than thirty minutes. Clinical observation indicates that at this rate the infant can metabolize the injected citrate rapidly enough to prevent hypocalcemia.[37] More rapid injection carries with it the danger of citrate shock, which cannot be entirely obviated by the injection of calcium gluconate.

Freshly drawn blood and bank blood have both proved to be satisfactory for the transfusion. Obviously, however, fresh blood is safer, since the blood cells are less fragile and the danger of bacterial contamination is virtually eliminated. When bank blood is used, it should be as fresh as possible, and preferably not more than three days old. Sedimented bank blood is more convenient for the preparation of concentrated blood, because all that is necessary is to aspirate the supernatant citrated plasma down to the 400 ml. mark. This should be done immediately before use. Then the bottle should be inverted and a sample should be withdrawn, centrifuged, and examined for hemolysis by observation of the supernatant plasma, as well as for bacteria by examination of a stained smear. Any sample of bank blood whose appearance or physical properties appear to be unusual should not be used for exchange transfusion.

When all of the precautions are scrupulously observed, the procedure is virtually without danger, and presents no greater hazard than an ordinary blood transfusion in an infant. In our method, where bleeding is accomplished by nicking the radial artery at the wrist and infusing blood through the saphenous vein at the ankle, the procedure is an open one which involves only expendable vessels. Should any difficulty be encountered with infusion, numerous other sites are available. The arteriotomy is always simple, although the neophyte may take a few minutes to locate the radial artery, if he is not familiar with its appearance and location. After the procedure is completed, the vessels need not be ligated, since bleeding is readily controlled by simple pressure bandages.

The umbilical catheter method introduced by Diamond,[38] though widely used, has not been employed by us. The method is simple and efficient, but carries with it the disadvantage that it is a blind procedure, and has been said to have caused damage to important intra-abdominal vessels with resultant thrombosis and embolism. Intra-abdominal hemorrhage, peritonitis, and splenic rupture have also been reported following its use. Since the position of the catheter tip is not visualized, there is the possibility of

direct injection of citrated blood into the heart chamber. Certainly the procedure is not shorter, and when the umbilical vessels cannot be catheterized, certain operators[39, 40] have had to resort to incisions in the abdominal wall and groin in order to catheterize large vessels in those regions.

RESULTS

For a valid comparison of results of treatment in a disease that shows the marked variability of erythroblastosis fetalis, it is necessary to be certain that the series of cases being compared are equal in severity. For this purpose various criteria such as the cord hemoglobin concentration,[41] the baby's capillary hemoglobin concentration, the cord bilirubin, the rate of rise of blood bilirubin, the erythroblast count, the quantitative direct antiglobulin test on the baby's cells,[17] the titer of antibody in the maternal and infant serum, and the physical findings such as hepatosplenomegaly and edema have been used.[42, 43] Methods of evaluating severity using the results of these various tests and criteria have not proved workable in most instances. Although it is true than an infant who shows anemia, edema, hepatosplenomegaly, and jaundice is unquestionably severely affected, many infants are born with none of these signs and still go on to develop severe disease and die. Obviously, any criterion of severity that requires longitudinal studies done on the baby and collected in retrospect cannot be used as a practicable indication for the need of treatment at birth or shortly thereafter.

Mollison and Cutbush[41] have shown that the hemoglobin concentration of the cord blood is of considerable value in assessing the severity of the disease, while the baby's capillary hemoglobin concentration immediately after birth varies, depending upon the time that the cord is clamped. Unfortunately, the hemoglobin concentration of the cord blood is not always available, particularly in babies seen some time after birth, when the cord blood has either been discarded or is already clotted. So far as bilirubin concentration is concerned, the rate of rise in the first few hours of life is a fairly good criterion of severity. However, when treatment has been given, these values are altered so that even in retrospect they are of little value, particularly in infants who have been treated by exchange transfusion. Erythroblastemia is generally of short duration, and might well be missed in cases seen late in the disease. Physical findings such as edema and hepatosplenomegaly, though frequently of grave prognostic import, are not necessarily present in infants who die of kernicterus or of pulmonary hemorrhage. Our own experience has demonstrated that the most reliable single criterion of severity in this disease is the maternal antibody titer at term.[6] It can be determined even in cases in which no antenatal studies have been done, and hence is practicable. Needless to say, its accuracy is increased if a survey of the titers obtained during the course of the pregnancy is also available, since the average of several titers is more accurate than a single determination, and therefore such an average is of even greater prognostic significance.

In a previous study,[33] our series was divided into four degrees of severity according to antibody titer. In the present paper, a simpler classification into only two categories has been

adopted, based on an analysis of a series of sensitized Rh-negative women who had had stillbirths. In Table I are given the Rh antibody titers of thirty-six Rh-negative women who had stillbirths apparently caused by Rh sensitization. It will be seen that with but a single exception all of these patients had antibody titers greater than 8 units by the albumin-plasma conglutination method. In order to compare the results of the various methods of treatment and the several modifications of treatment with exchange transfusion, cases with titers below 8 units were therefore analyzed separately from those with titers above 8 units. Griffitts[33a] has used a similar criterion of severity, but based on titrations by the antiglobulin method.

TABLE I. RH ANTIBODY TITERS (BY ALBUMIN-PLASMA CONGLUTINATION METHOD) IN RH-NEGATIVE WOMEN HAVING STILLBIRTHS*

ANTIBODY TITER† (UNITS)	NUMBER OF PATIENTS
0	1‡
−1	0
−2	0
−4	0
−8	0
−16	3
−32	8
−64	8
−128	11
−256	2
−512	1
−1024	2

*This table includes only patients studied during the past two or three years. For previous statistics on stillbirth rates in sensitized Rh-negative women, see Wiener and associates[6].

†Antibody titer −8, for example, represents all cases with titers by the albumin-plasma conglutination method greater than 4 units and up to and including 8 units, and similarly for the other titer values.

‡In this exceptional case, the antibody titer by the antiglobulin method was 64 units, and 160 units by the method using enzyme-treated test cells. Apparently, the antibody was of exceptional type, which gave no clumping in vitro by the albumin-plasma conglutination method.

In Table II are summarized the results of different methods of treatment of erythroblastosis classified according to severity, as indicated by the maternal antibody titer at term. The superiority of exchange transfusion over expectant treatment and simple transfusion therapy is most apparent in the more severely affected infants, namely, those whose mothers had antibody titers over 8 units. In this group there were twenty-eight babies who were treated with expectant therapy or with simple transfusion, of whom thirteen died or had neurological sequelae, a "mortality" rate of 46.4 ± 6.2 per cent.* On the other hand, among 154 infants treated by exchange transfusion in the above 8 unit titer group, there were twenty-four deaths or neurological sequelae, a mortality rate of 15.5 ± 2.0 per cent. The difference, 28.9 ± 6.5 per cent is statistically significant. In the series comprising the more mildly affected infants the method of treatment appeared to make little or no difference, as might be expected, since in general these babies would be expected to do well. Thus, among thirty-nine such babies treated expectantly or by simple transfusion only one baby died, a mortality rate of only 2.5 ± 1.6 per cent, while among sixty-eight similar babies treated by exchange transfusion five died, a mortality rate of 7.3 ± 2.0 per cent. Here, the difference, 4.8 ± 2.5 per cent, is not significant statistically.

A word might be in order at this point concerning our own bias in choosing the cases that were to be treated by exchange transfusion, and those treated expectantly or by simple transfusion. In general, the antibody titer of the maternal serum by the albumin-plasma method was used as the guide, although clinical symptoms and

*The figure following the ± sign represents probable error.

other laboratory findings were always taken into account. If there was any doubt as to the wisest course, exchange transfusion was resorted to. This might seem to favor exchange transfusion in the selection of cases. On the other hand, when the titer was low and the symptoms mild, we treated the child expectantly, and this type of selection would tend to favor the group which received expectant treatment. However, in the group which received expectant treatment there are also many instances of infants who were not treated by us, and were seen by us only after the children were either moribund or it was too late in the disease to expect any good result from exchange transfusion. These may be regarded as a selected group of more severely affected babies, and would favor exchange transfusion in the statistical analysis. In any event, even assuming some bias in the selection of the cases, the results clearly indicate the relationship of the maternal antibody titer to the severity of the disease, and the superiority of exchange transfusion for its treatment. To our knowledge, Mollison and associates[44, 45] are the only workers who were able to carry out a controlled comparison of exchange transfusion and simple transfusion, in which the type of treatment to be used in each individual case was decided by lot. Their results show the superiority of exchange transfusion as did earlier analyses of our own material.[36, 46]

TABLE II. COMPARISON OF RESULTS OF DIFFERENT METHODS OF TREATING ERYTHROBLASTOSIS FETALIS*

METHOD OF TREATMENT	MATERNAL ANTIBODY TITER 8 UNITS OR LESS†			MATERNAL ANTIBODY TITER ABOVE 8 UNITS		
	TOTAL NUMBER OF BABIES	MORTALITY‡		TOTAL NUMBER OF BABIES	MORTALITY	
		NUMBER	% ± P. E.		NUMBER	% ± P. E.
None	20	1	5.0 ± 3.2	9	5	55.6 ± 11.0
Simple transfusion	19	0	0.0	19	8	42.1 ± 7.5
Exchange transfusion						
(a) 500 ml. citrated blood	19	2	10.5 ± 4.2	46	10	21.7 ± 3.8
(b) 1,000 ml. citrated blood	11	2	18.2 ± 7.6	38	6	15.5 ± 3.8
(c) 150 ml. packed cells	13	1	7.7 ± 4.9	17	4	23.1 ± 4.6
(d) 400 ml. concentrated blood	22	0	0.0	44	3	6.8 ± 2.6
(e) Double exchange	3	0	0.0	9	1	11.1 ± 6.6

*This includes only cases caused by Rh sensitization.
†By albumin-plasma conglutination method.
‡Mortality includes not only deaths, but also babies with neurological sequelae.

As for the different modifications of exchange transfusion used by us, the difference in mortality rate, while not striking, suggests the superiority of the present method of therapy, using blood from which part of the citrated plasma has been removed. Among seventy-eight affected babies treated by this technique only three died, while one survived with neurological sequelae, a total mortality rate of only 5.1 ± 1.6 per cent, even though more than two-thirds of these babies were severely affected (cf. Table II).

ILLUSTRATIVE CASE REPORTS

Several cases of unusual interest, or which serve to emphasize important general principles, will now be described in detail.

CASE 1.—*Four pregnancies yielding three erythroblastotic babies, each treated by a different modification of exchange transfusion.*

The mother of this family was first studied during her second pregnancy, when she was found to be Rh negative and sensitized to the Rh factor. She had never received a blood transfusion, and her first pregnancy terminated on April 17, 1948, with the birth of a normal female child. Her second pregnancy yielded an erythroblastotic infant, as was predicted, based on the presence of Rh sensitization. This baby and two subsequent erythroblastotic babies born in 1951 and 1953, respectively, were all treated by a different modification of exchange transfusion. The grouping and Rh-Hr tests on the parents and four children are shown in Table III.

TABLE III. RESULTS OF GROUPING AND RH-HR TESTS ON FAMILY OF CASE 1

BLOOD OF	A-B-O GROUP	M-N TYPE	RH-HR TYPE	
			PHENOTYPE	GENOTYPE
Father	A_1	MN	Rh_1Rh_2	R^1R^2
Mother	A_1	MN	rh	rr
First child ♀ (normal)	A_1	MN	Rh_1rh	R^1r
Second child ♀ (erythroblastotic)	A_1	MN	Rh_2rh	R^2r
Third child ♂ (erythroblastotic)	A_1	M	Rh_1rh	R^1r
Fourth child ♀ (erythroblastotic)	A_1	MN	Rh_1rh	R^1r

With regard to the Rh antibody titer during the second, third, and fourth pregnancies, while the techniques of titration used underwent some changes during the period 1949 to 1953, the albumin-plasma conglutination method was used throughout and can be used as a basis of comparison. The results of these studies have been summarized in Table IV, from which the trend of the antibody titers can be visualized.

As shown in Table IV, the antibody titer during the last three months of the second pregnancy showed no tendency to rise,* the average titer by the albumin-plasma conglutination method being about 40 units. Nor was there any rise in titer after the second baby was born. Likewise, during the third pregnancy the antibody titer remained constant, the average titer by the albumin-plasma method this time being about 20 units. Moreover the post-partum antibody test after the third pregnancy showed no significant rise in titer. Even though the titer by the albumin-plasma method was found to be 80 units, this probably represents an accidental technical variation, considering that the other methods of titration showed no comparable rise in titer.) During the fourth pregnancy again the antibody titer showed no tendency to rise, the average titer by the albumin-plasma method this time being only 7 units. Apparently during the four-year period which followed the second pregnancy, there had been a gradual decline in titer from 44 units to 7 units. This indicates that during the third and fourth pregnancies there had been no appreciable leakage of fetal blood into the maternal circulation to stimulate a rise in the Rh antibody titer, and with the passage of time a gradual decline in titer is to be expected. However, following the fourth pregnancy there was a significant rise in titer, indicating that during this delivery some fetal blood must have entered the

*In view of the intrinsic limits of error of the titration technique, any deviation from the average titer by less than one dilution should not be considered significant. Thus, with an average titer of 44 units, values ranging from 22 to 88 units are within the limits of error of the method. In fact, anything less than a fourfold deviation in titer from the average could well be accidental.

maternal circulation. Summarizing, the results show a gradual decline in the antibody titer from the second to the fourth pregnancy, so that from this point of view, one would expect that the baby born after the fourth pregnancy would be the least severely affected of the three erythroblastotic babies.

As shown in Table V, the third erythroblastotic baby was indeed the least severely affected of the three babies, in conformity with the prediction based on the antenatal Rh antibody titers. In fact, this baby might have been passed over as normal and left untreated had we not been forewarned and forearmed by the serological tests. There was not much difference in the degree of severity between the first two affected babies, though the findings on the second were somewhat milder, corresponding to the slightly lower antibody titer.

TABLE IV. Rh ANTIBODY TITERS IN THE MATERNAL SERUM (CASE 1) DURING AND AFTER THE SECOND, THIRD, AND FOURTH PREGNANCIES

TIME OF TEST	ANTIBODY TITER (UNITS*) BY METHOD OF: AGGLUTINATION	BLOCKING	ALBUMIN-PLASMA CONGLUTINATION	ANTIGLOBULIN	ENZYME-TREATED CELLS	COMMENT
During second pregnancy						
4/ 4/49	0	—†	24	—	—	
5/25/49	0	2	50	—	—	
6/29/49	0	½	60	384	—	
7/12/49	0	2	44	88	—	Labor induced
Average	0	1½	44	236	—	No significant change in titer during this pregnancy
8/15/49 (post partum)	0	3	56	—	—	No post-partum rise in titer
During third pregnancy						
10/24/50	0	3	28	—	95	
1/10/51	0	2	24	—	56	
2/ 4/51	0	3	10	—	78	
3/ 7/51	0	1	24	—	96	
3/19/51	0	1	14	—	77	Labor induced 3/20/51
Average	0	2	20	—	80	No significant change in titer during pregnancy
3/31/51 (post partum)	0	3	80	—	160	No significant rise in titer post partum
During fourth pregnancy						
5/14/53	0	½	4	16	32	
6/25/53	0	—	3	36	42	
7/31/53	0	½	6	34	80	
9/ 1/53	0	--	14	36	30	
10/ 3/53	0	—	—	64	32	
10/21/53	0	—	—	92	56	
10/28/53	0	—	—	54	32	
11/14/53	0	--	--	48	28	Labor induced 11/7/53
Average	0	½	6	48	43	No significant rise in titer during pregnancy
11/19/53 (post partum)	0	—	40	246	192	Significant post-partum rise in titer

*The titer in units is the reciprocal of the highest serum dilution giving a distinct (one plus) reaction. For technique of test see Wiener and associates.[9]

†Tests not done.

TABLE V. FINDINGS ON THREE ERYTHROBLASTOTIC BABIES (CASE 1)

	RESULTS OF TESTS FOR COATING OF RED CELLS			FREE RH ANTIBODIES					
BLOOD OF	BLOCKING	CONGLUTINATION	ANTIGLOBULIN	AGGLUTINATION	ALBUMIN-PLASMA CONGLUTINATION	ANTIGLOBULIN	ENZYME-TREATED CELLS	CORD ICTERUS INDEX	HEMOGLOBIN CONCENTRATION AT BIRTH (GM.)
First affected baby	Completely blocked*	Strongly positive	Strongly positive	0	6	16	—	50	10.5
Second affected baby	Completely blocked	Strongly positive	Strongly positive	0	0	—	10	40	10.5
Third affected baby	—	—	90%†	0	0	½	8	32	19.5

*Cells failed to clump in tests for the Rh_0 factor in the saline agglutination method.
†Results of quantitative direct antiglobulin test.

The first affected baby was treated by exchange transfusion, using 1,000 ml. of citrated blood. The second affected baby was given an exchange transfusion using 120 ml. of packed cells. The third affected baby was given two exchange transfusions twenty-four hours apart, using bank blood which had been stored in ACD solution, and from which part of the citrated plasma was removed, reducing the total volume to 400 ml. The first and third affected babies recovered completely and are entirely normal today, but the second baby died shortly after birth, despite the exchange transfusion.

A terse summary of the clinical course of each baby may be instructive.

First affected baby. She was first given 35 ml. of packed cells, after which the hemoglobin concentration rose from 10.5 to 18 Gm. The exchange transfusion was then completed in the usual way, 850 ml. being injected while 750 ml. were removed. Despite the transfusion the baby became deeply jaundiced at forty-eight hours and the temperature rose to 101° F. However, the blood count was maintained and the jaundice then faded rapidly, so that the baby could be discharged with her mother on the seventh day. Subsequent physical and mental development have been entirely satisfactory.

Second affected baby. He was treated by withdrawing 120 ml. of blood and injecting 120 ml. of packed cells. The hemoglobin concentration rose to 19.2 Gm., but the baby became deeply jaundiced, and three days after the transfusion was performed, the jaundice became much deeper, the baby passed bright red blood by mouth, and became cyanotic and dyspneic. The baby expired without developing anemia.

Third affected baby. This baby was given an exchange transfusion, using 400 ml. of concentrated blood. Following the transfusion the hemoglobin concentration rose to 24 Gm., and though noticeable jaundice appeared, the baby remained active and well. Differential agglutination showed that about 15 per cent of the baby's coated cells were still present, and because of the death of the previous affected baby, a second exchange transfusion was carried out. The jaundice then disappeared within forty-eight hours and the subsequent course was uneventful.

Case 1 is of interest in showing the course which antibody titers may follow over a period of years, during a number of successive pregnancies. Moreover, this case demonstrates that the classic description of erythroblastosis as a disease affecting successive babies with progressively increasing severity does not always hold. This must be taken into account when evaluating the use of drugs, such as cortisone, for the antenatal management of the disease. In this case there was a striking correlation between the height of the antibody titers and the severity of the manifestations in the affected babies, but one must bear in mind that such a perfect correlation does not obtain in every case. Finally, as has been pointed out, the results indicate the inferiority of simple transfusions of packed cells, and the importance of replacing the baby's coated cells as completely as possible when carrying out an exchange transfusion.

CASE 2.—*Five pregnancies yielding one normal baby, one spontaneous abortion, and three erythroblastotic babies.*

We were asked to see the second baby in this family when he was 3 days old, because he was deeply jaundiced. At birth this male infant had appeared normal and had had no anemia or jaundice. By the second day, however, jaundice appeared and this became pronounced by the third day, though there was no drop in hemoglobin concentration. At this time, our tests showed the mother to be Rh negative and only mildly sensitized to the Rh factor. Moreover, the direct antiglob-

ulin test on the baby's cells was only weakly positive, so that the baby, though erythroblastotic, appeared to be only mildly affected. Expectant treatment was advised. The jaundice rapidly cleared and there was a gradual drop in blood count, so that at one month of age, the hemoglobin concentration was 7.5 Gm. The baby was treated with two simple transfusions of packed cells, recovered completely, and is now entirely well.

The mother of this baby had never received a blood or plasma transfusion which might have sensitized her. The first pregnancy had yielded a perfectly normal male infant. We subsequently followed her through three additional pregnancies, two of which yielded erythroblastotic babies, while one terminated in a spontaneous abortion. The results of the grouping and Rh-Hr tests on the entire family are shown in Table VI.

TABLE VI. RESULTS OF GROUPING AND RH-HR TESTS ON FAMILY OF CASE 2

BLOOD OF	A-B-O GROUP	M-N TYPE	RH-HR TYPE	
			PHENOTYPE	GENOTYPE
Father	O	MN	Rh_2Rh_2	R^2R^2 or R^2r''
Mother	B	MN	rh	rr
First child ♂ (normal)	B	MN	Rh_2rh	R^2r
Second child ♂ (erythroblastotic)	O	MN	Rh_2rh	R^2r
Third child ♀ (erythroblastotic)	B	N	Rh_2rh	R^2r
Fourth child (hydropic)	B	MN	Rh_2rh	R^2r

The course of the maternal Rh antibody titers during the subsequent pregnancies is shown in Table VII. Shortly after the birth of the second baby, i.e.,

TABLE VII. RESULTS OF TITRATIONS OF MATERNAL RH ANTIBODIES IN CASE 2

TIME OF TEST	ANTIBODY TITER (UNITS) BY METHOD OF				REMARKS
	AGGLUTINATION	ALBUMIN-PLASMA CONGLUTINATION	ANTI-GLOBULIN	ENZYME-TREATED CELLS	
After second pregnancy					
6/14/49	0	1½	3	—	Four days after birth of second baby
6/23/49 (post partum)	0	2½	2½	—	No post-partum rise in titer
Third pregnancy June, 1950	—	—	—	—	Spontaneous abortion at 2 months
During fourth pregnancy					
9/20/51	0	1	—	10	
10/18/51	0	0	—	10	
11/ 3/51	0	½	—	38	
11/10/51	0	½	—	44	
11/21/51	0	0	—	36	
11/30/51	0	2½	11	37	Day of delivery
Average	0	1	11	29	No significant change in titer during pregnancy
12/20/51 (post partum)	0	4	80	120	Significant post-partum rise in titer
During fifth pregnancy					
5/21/53	0	1	20	36	
6/25/53	0	2	—	64	
7/30/53	0	1½	18	52	
8/13/53	0	6	24	56	
8/20/53	0	0	21	30	
8/26/53	0	1½	9	28	
9/ 2/53	0	9	19	40	Day of delivery
Average	0	3	18	44	

TABLE VIII. FINDINGS ON THE THREE ERYTHROBLASTOTIC BABIES OF CASE 2

	COATING OF RED CELLS			FREE RH ANTIBODIES					
BLOOD OF	BLOCKING	CONGLUTINATION	ANTIGLOBULIN	AGGLUTINATION	ALBUMIN-PLASMA	ANTIGLOBULIN	ENZYME-TREATED CELLS	CORD ICTERUS INDEX	HEMOGLOBIN CONCENTRATION (GM.)
First baby	Neg.	Neg.	Weakly positive	—	—	—	—	—	16.9
Second baby	Neg.	Neg.	Positive moderately strong	0	½	—	20	28	12.0
Third baby*	Neg.	—	Positive	0	0	0	8	20	6.7

*Baby hydropic and died one hour after birth.

the first affected baby, the maternal Rh antibody titer was very low, and there was no rise in titer during the post-partum period. The third pregnancy, one year later, terminated in an early abortion, and this had no apparent effect on the maternal Rh antibody titer. During the fourth pregnancy, the Rh antibody titer was again found to be low. However, after the birth of the third baby at the end of the fourth pregnancy, there was a post-partum rise in Rh antibody titer, namely, a fourfold increase. The fifth pregnancy occurred two years later, and in the interim the antibody titer had slipped back somewhat, so that the titers were only twice as high as during the fourth pregnancy. This rather low titer was maintained with no significant change until term, when the third erythroblastotic baby was born.

Table VIII shows the hematological findings on the three erythroblastotic babies. As has already been pointed out, the first affected infant exhibited only mild symptoms of erythroblastosis. In the second affected baby the manifestations were also mild, though more severe than in the first. This baby was treated by exchange transfusion using 400 ml. of concentrated blood, and recovered completely without further treatment. During the fifth pregnancy, in view of the higher antibody titers, we expected a somewhat more severely affected baby. However, considering that the titers, though higher than previously, were still low, we thought that the baby would not be too severely affected. Much to our surprise the baby was born with a severe anemia, had a markedly enlarged liver and spleen, and was hydropic. No treatment was attempted since this would obviously be of no avail, and the baby died within an hour after birth.

This case is classical in demonstrating the increasing severity of the manifestations in successive erythroblastotic babies. One remarkable finding was the low titer of maternal antibodies which was sufficient to cause the birth of a hydropic baby, who survived only one hour. Nevertheless, within the family proper there was a correlation between antibody titer and severity of manifestations. The case also demonstrates again the superiority of exchange transfusion over simple transfusion, in bringing about prompt recovery and shortening the period of observation required.

CASE 3.—*Seemingly mild erythroblastosis treated expectantly, with resulting neurological sequelae.*

This patient was studied antenatally during her third pregnancy because she was known to be Rh negative and sensitized to the Rh factor. She had never received a blood or plasma transfusion, and her obstetrical history was as follows. Five years previously she had given birth to her first baby, who was born at term and had no neonatal anemia or jaundice. Her second pregnancy terminated four years before with a miscarriage at the fifth month.

The patient herself belonged to group O, type rh, while her husband belonged to group A, type Rh_1Rh_2. The mother's Rh antibody titer was very low, the average of four antibody titrations being only ½ unit by the albumin-plasma conglutination method, 3 units by the antiglobulin method, and 10 units by the enzyme-treated-cells method. Labor was induced at term and a normal-appearing baby was delivered. The baby proved to belong to group O, type Rh_2rh. The direct antiglobulin test was only weakly positive (one plus), as was to be expected in view of the mother's low antibody titer. The hemoglobin concentration was 22 Gm., and there were 8 normoblasts per 100 white blood cells. The only abnormal finding was the icterus index of the cord serum, which proved to be 32 units. In view of the high blood count and insignificant serolog-

ical findings, it was decided to treat the baby expectantly. The higher than normal icterus index of the cord serum by itself at the time did not seem a sufficient indication for an exchange transfusion.

During the first three days of life the blood count was maintained, but clinical jaundice appeared within eighteen hours and became progressively deeper. On the fourth day the jaundice became very deep, there was a rise in temperature to 103° F., the baby became lethargic, and exhibited stiffness of the neck for a short time. It was then quite obvious that the baby had nuclear jaundice. The jaundice persisted for two weeks. At no time did the baby require a blood transfusion, since the lowest value to which the hemoglobin concentration dropped was 10.5 Gm. When the baby was seen again at the end of six months, he exhibited retardation in development, and he was unable to hold his head up without support.

The importance of this case is that it demonstrates that there are exceptions to the correlation between antibody titer and severity, and that a high hemoglobin concentration at birth does not necessarily imply a good prognosis. Thus, it is not possible to predict with certainty the outcome of any individual case. It also demonstrates the importance of treating every affected baby by exchange transfusion, even when the initial manifestations are mild, not only to prevent death but especially to prevent neurological sequelae in surviving babies. Elevation of the icterus index itself appears to be a very strong indication for exchange transfusion, even in the absence of anemia and despite minimal serological findings.

CASE 4.—*Erythroblastosis treated by two exchange transfusions; complete recovery despite hemolysis of bank blood.*

The patient was referred at the end of the fourth pregnancy, because she had been found to be Rh negative and sensitized to the Rh factor. She had three normal children. Her type proved to be O MN rh, while her husband's type was O MN Rh_1rh. Antibody titrations carried out by another laboratory gave values of 2 units two months before term, rising to 32 units shortly before we saw the patient for the first time. The average of two titrations carried out by us gave the following results: agglutination method—negative, albumin-plasma conglutination method—4 units, antiglobulin method—75 units, and enzyme-treated-cells method—200 units.

The baby was born at term and was promptly referred to us for treatment. The baby's type proved to be O MN Rh_1rh, and the direct antiglobulin test was positive, the degree of coating being approximately 30 per cent. The hemoglobin concentration was 18.5 Gm., with 11 normoblasts per 100 white blood cells on the smear, but the icterus index of the cord serum was 32 units.

TABLE IX. ANTENATAL RH ANTIBODY TITERS OF THE MATERNAL SERUM IN CASE 3

	ANTIBODY TITER (UNITS) BY METHOD OF				
DATE OF TESTS	AGGLUTINATION	ALBUMIN-PLASMA CONGLUTINATION	ANTIGLOBULIN	ENZYME-TREATED CELLS	COMMENT
4/ 5/52	0	1	3	12	
4/29/52	0	0	2½	9½	
5/ 6/52	0	0	—	3½	
5/13/52	0	0	—	14	One week before birth of baby
Average	0	¼	3	10	

An exchange transfusion was performed, using 400 ml. of concentrated blood.

Following the exchange transfusion, the hemoglobin concentration rose to 19.8 Gm., but the baby exhibited progressively increasing jaundice, the icterus index rising to 160 units at the end of forty-eight hours. Because of the deepening jaundice, a second exchange transfusion was carried out when the baby was 3 days old, using three-day-old bank blood, which had been concentrated to 400 ml. by removing part of the plasma. At the end of this procedure the baby became apathetic. A short time later he passed very dark red, almost black, urine, which, however, looked clear when held up to light. The urine contained no red cells, but spectroscopic examination showed the presence of free hemoglobin. The baby was then placed on a restricted fluid intake, in order to guard against hemoglobinuric nephrosis. There was diminished urinary output, but the hemoglobinuria cleared within twenty-four hours, and the urea nitrogen rose to only 30 mg. per 100 ml. one day after the transfusion. The jaundice cleared rapidly despite the hemolytic episode, and the baby appeared well within a few days, except for pallor. The blood count taken at this time showed a hemoglobin concentration of only 11.7 Gm. This was corrected by the transfusion of 60 ml. of packed cells, and the subsequent course was uneventful.

The hemolytic transfusion reaction in this case was shown not to be due to any obscure incompatibility. The most reasonable explanation seemed to be the use of bank blood which had been inadvertently frozen during storage and then thawed again. This experience emphasizes the importance of being certain that bank blood used for exchange transfusion is fresh, and that a sample is removed from the bottle and centrifuged, in order to detect the presence of hemolysis. Bank blood which exhibits any unusual behavior should not be used.

It is significant that despite the massive hemolysis the icterus index fell rapidly after the second transfusion. This is further evidence that jaundice in erythroblastosis is not due to hemolysis but to liver damage. Liver damage, in our opinion, is due to intravascular conglutination, which exchange transfusion prevents.

Some workers[43] ascribe the beneficial results of exchange transfusion to the supposed removal of large amounts of free antibody in the baby's blood. Actually, the amount of antibody removed is relatively small, since antibody present in the tissue juices, which is not removed by exchange transfusion, later diffuses into the baby's circulation. In the present case, for example, the titer of free Rh antibodies in the baby's plasma for enzyme-treated cells proved to be as follows:

Time of test	*Titer (units)*
At birth: cord serum	61
Before first exchange transfusion	59
At end of first exchange transfusion	32
3 days later	
Before second exchange transfusion	49
At end of second exchange transfusion	13
5 days after birth	27

As shown above, two exchange transfusions, sufficient to bring about a 98 per cent replacement of the baby's red cells, produced only a 50 per cent reduction in the titer of the free Rh antibodies in this baby's serum. Thus, the amount of Rh antibody removed from the baby is not sufficient to account for the beneficial effects of the exchange transfusion. Instead, as has already been pointed out, this depends on the removal of the baby's coated red cells and their replacement with cells incapable of reacting with the antibody remaining behind in the baby's body.

DISCUSSION

Our experience as well as the experience of others[43, 44, 45] has demonstrated the superiority of exchange transfusion over all other methods of treating erythroblastosis fetalis. Moreover, our results have undergone a distinct improvement in recent years. This can be attributed to several factors, especially the use of concentrated blood and the policy of repeating the exchange transfusion in the more severely affected babies. By using concentrated blood (hematocrit 0.50) it is possible to attain a high hemoglobin concentration even though the same volume of blood is injected as is withdrawn. Since there is no marked change in blood volume there is little or no circulatory strain for the baby. Probably a more important factor is the removal of a considerable amount of the ACD solution and plasma. This minimizes the toxic effect of citrate, which is then further counteracted by fractional injections of calcium gluconate during the procedure. The removal of part of the plasma also serves to reduce the amount of adult plasma that the baby receives, and this appears to be desirable, at least theoretically, since adult plasma contains a higher concentration of conglutinin and complement than does the plasma of the newborn infant. When carried out in this way, using the saphenous vein-radial artery technique, the procedure appears to be innocuous, as evidenced by the normal behavior of the infant during the procedure. Nevertheless, an attempt is made to avoid completing the procedure in less than thirty minutes.

In view of the excellent results of treatment by exchange transfusion and the safety of the procedure when carried out as described, our tendency has been to widen the indications for its use. Whenever the maternal antibody titer is above 8 units by the albumin-plasma technique, and the baby proves to be Rh positive, we feel that exchange transfusion is indicated no matter how normal the baby may appear to be at birth, and even if the hemoglobin concentration and icterus index are within normal limits. Obviously, if the maternal antibody titer is high and the baby is Rh positive, the direct antiglobulin test on the baby's red cells must be strongly positive, unless some laboratory error has been committed. If the maternal antibody titer is low, exchange transfusion should nevertheless be carried out if the baby exhibits any or all of the following: cord icterus index 20 units or over, hemoglobin concentration below 15 Gm., and a strongly positive direct antiglobulin test. In families where there have already been one or more severely affected erythroblastotic infants, the indications for immediate exchange transfusion on the newborn infant are even less rigid. A strong indication for exchange transfusion is a primipara who has been sensitized by a blood transfusion or blood injection, since inadequate treatment may deprive her of her only chance to have a viable baby.

The indications for performing a second exchange transfusion are still not clearly defined. We feel that it should be considered in cases where a previous erythroblastotic baby has been lost and/or the Rh antibody titer has been extremely high. In the absence of these two indications we feel that a second exchange transfusion is indicated whenever the baby has severe manifestations at birth, or when fol-

lowing the first transfusion the baby develops progressively increasing jaundice. We try if possible to time the second transfusion about twenty-four to forty-eight hours after the first one, in order to remove any newly appearing Rh-positive red blood cells, and in that way increase the efficiency of the second exchange.

According to our concept, nuclear jaundice and neurological sequelae represent disseminated brain damage resulting from intravascular conglutination of red cells blocking the circulation to the basal nuclei. However, it is now accepted that there is a correlation between the depth of jaundice exhibited by the erythroblastotic baby and the chance of nuclear jaundice.[47, 48] Therefore, Allen and associates[48] have adopted the policy of repeating the exchange transfusion in all babies exhibiting deep jaundice in an attempt to keep the bilirubin concentration in the blood below 20 mg. per 100 ml. We believe, however, that there is nothing to be gained by performing more than two exchange transfusions, since after the second the number of baby's coated red cells remaining in circulation is negligible.

With regard to the time of delivery, theoretically the baby should be delivered at the earliest possible time, in order to limit the period of exposure to the maternal Rh antibodies, and so that treatment can be instituted as soon as possible. However, if the baby is delivered too early, the hazards of prematurity will be added to those of Rh sensitization. Therefore, we have made it a policy whenever possible to deliver the baby about two weeks before term; at any rate, an effort is made to avoid postmaturity. With regard to the method of delivering the baby, cesarean section carries with it added hazards for the baby as well as the mother, so that this should never be resorted to unless there is a strong obstetrical indication for the operation. If conditions are ripe for delivery per vaginam, an attempt may be made to bring on labor but without rupturing the membranes. If this fails, the attempt may be made again at a later date rather than resort to more radical procedures for delivering the infant.

Mollison and Cutbush[41] have advocated the use of hemoglobin concentration of cord blood as a criterion of severity in erythroblastosis fetalis. They have found a strong correlation between hemoglobin concentration and the probability of survival, almost all the fatal cases occurring in infants with values below 10 Gm., and none, or hardly any, in those with values above 15 Gm. Their tendency, therefore, was to withhold treatment in erythroblastotic babies having hemoglobin concentrations above 15 Gm., but this policy proved to be unsatisfactory. The incidence of neurological sequelae when treatment was withheld proved to be 7 per cent in mature infants and as high as 16 per cent in immature infants.[45] Armitage and Mollison[45] felt that most, if not all, of these infants would have developed normally had they been treated by exchange transfusion. Our Case 3 illustrates the unfortunate outcome when treatment is withheld merely because the blood count is normal.

SUMMARY

Among thirty-six stillbirths caused by Rh sensitization, all but one of the patients had Rh antibody titers of 16 units or higher by the albumin-plasma

conglutination method. (In the single exceptional case, where the albumin-plasma titrations were negative, it was possible to show that antibodies were present, but of an unusual type, since the titer was high by the antiglobulin and enzyme techniques.) Therefore, when using antibody titer as a criterion of severity, it was decided to consider 8 units by the albumin-plasma titration method as the upper limit for cases classified as "mildly" affected.

The results of treatment by exchange transfusion in a series of 222 erythroblastotic infants were compared with the results obtained in a series of sixty-seven erythroblastotic babies who were left untreated or given one or more simple transfusions. Among "mildly" affected babies, i.e., those whose mothers had antibody titers of 8 units or less, no significant difference in the mortality rate in the two series was demonstrable. On the other hand, among severely affected babies treated by exchange transfusion, the mortality rate was 15.5 ± 2.0 per cent, while among the babies receiving simple transfusions or no treatment, the mortality rate was as high as 46.4 ± 6.2 per cent. The difference in mortality rate, 28.9 ± 6.5 per cent, is statistically significant.

During the past few years changes have been introduced into our method of carrying out exchange transfusions. In the method now used by us, part of the citrated plasma is removed from bank blood not more than three days old, which has been allowed to sediment in the refrigerator in order to reduce the volume to 400 ml., and the resulting concentrated blood (hematocrit, approximately 0.50) is used for the exchange transfusion, equal volumes of blood being withdrawn and injected. In more severely affected babies, a second such exchange transfusion is given twenty-four to forty-eight hours after birth. Among seventy-eight erythroblastotic babies treated in this way, of whom fifty-three had mothers with antibody titers above 8 units by the albumin-plasma method, the mortality rate was only 5.1 ± 1.6 per cent. (In this discussion, mortality rate is used to include neurological sequelae as well as deaths.)

Case reports are presented in order to illustrate the course of Rh sensitization in women followed through several pregnancies and to compare the results of treatment of several erythroblastotic babies born to the same mother. A case is cited which demonstrates the importance of icterus per se as a criterion of severity, and therefore this sign is a strong indication for treatment by exchange transfusion even in the absence of anemia.

In view of the innocuousness of exchange transfusion carried out by the radial artery-saphenous vein technique and the excellent results obtained by this treatment, our tendency has been to widen the indications for its use in treating erythroblastotic babies.

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NUCLEASES IN THE CEREBROSPINAL FLUID

II. Desoxyribonuclease in Health and Disease

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ENZYMIC degradation of highly polymerized desoxyribonucleic acid (DNA) is brought about by desoxyribonuclease (DNA-se), or nucleo-depolymerase.[18, 20] Araki[1] and Sachs[19] were the first to demonstrate hydrolysis of DNA. Following the work of many biochemists[10, 15, 16, 21] the present conception of stepwise decomposition has been accepted. Greenstein and co-workers,[3, 4] McCarty,[18] and Little and Butler[17] completed the efforts of previous workers with basic theoretical and technical contributions. Kunitz[14] succeeded in isolating crystalline DNA-se from pancreas, and introduced a spectrophotometric technique for measurement of its activity. During our studies of nucleic acids (NA)[12] and their fermentative splitting,[11] we were able to detect ribonuclease (RNA-se) in the cerebrospinal fluid (CSF). The present paper is a report of DNA-se in CSF of normal and pathological cases.

METHODS

The viscosimetric technique,[4] as modified by McCarty,[18] was adapted to our purpose. DNA-se activity was indicated by the drop in viscosity of the substrate-CSF mixture. Highly polymerized DNA* served as substrate in 0.1 per cent solution in borate buffer of pH 7. Three-tenths milliliter of centrifuged, fresh or freshly frozen CSF was added as enzyme material. $MgSO_4$ was used as activator in 0.003 M final concentration, and commercial gelatin solution as stabilizer in 0.01 per cent final concentration. Each new batch of substrate was assayed with purified DNA-se of pancreas.

Routine of the Experiments.—Incubation was carried out in an electrically controlled water bath, assuring constant temperature of 30° C. Four and seven-tenths milliliters of substrate containing magnesium and gelatin was thoroughly mixed with 0.3 ml. of CSF, and put into the viscosimeter. Readings of the flow were taken at five-minute intervals for sixty minutes with a stop watch. The Ostwald pipette was calibrated with distilled water and the relative viscosity of the system calculated.

Controls.—The viscosity of the substrate was measured several times before mixing in every set of experiments, with and without magnesium and gelatin, to check the reactivity of the ingredients. Heat-inactivated CSF, physiological saline, or distilled water was run occasionally with substrate to exclude any nonspecific decrease of viscosity.

Other Techniques.—DNA-se activity of the CSF was checked by other methods as follows. Decrease of acid precipitability,[17] using King's method for acid soluble phosphorus[9]; acid precipitation, followed by spectrophotometry of the fitrate[14]; direct measure-

From Department of Hygiene and Preventive Medicine, University of Toronto. This work was financed through a Mental Health Grant.

*Kindly supplied by Prof. G. C. Butler, Department of Biochemistry, University of Toronto.

ment of the change in optical density of the system,[14] were compared occasionally with routine viscosimetry. The effects of various factors were investigated, namely, substrate and enzyme concentration, buffers and pH ranges, activators and inhibitors, and temperature of incubation. The effect of room and refrigerator temperatures and the influence of deep freezing on the CSF were studied. Sterile routine was strictly observed in the handling of ingredients. Beckman model DU ultraviolet spectrophotometer, with quartz cells of 1 cm. light-path, was used for density readings.

TABLE I. DNA-SE DETERMINATIONS IN 200 CEREBROSPINAL FLUIDS (VISCOSIMETRIC METHOD)

GROUP	NUMBER OF CSF'S	RANGE OF DROP IN FLOW TIME IN SECONDS	AVERAGE	DNA-SE ABSENT IN PER CENT OF SPECIMENS
1. Normal and neurologically normal	50	0-10	1.1	45
2. Meningitides	50	0-123	29.9	10
3. Poliomyelitis and other virus diseases	50	0-0	0.0	100
4. Syphilis, neurosyphilis, and miscellaneous neurological and psychotic group	50	0-299	23.0	10

TABLE II. GROUP A: EXAMPLES OF DNA-SE ACTIVITY MEASURED BY INCREASE OF ACID-SOLUBLE PHOSPHORUS

Purified DNA-se of pancreas	0.2 μg	14.04 mg. %
Normal specimen	0.3 ml. CSF	No change
Meningococcal meningitis specimen	0.3 ml. CSF	12.00 mg. %
Paralytic polio specimen	0.3 ml. CSF	No change
Latent syphilis specimen	0.3 ml. CSF	2.2 mg. %
Paranoia specimen	0.3 ml. CSF	6.0 mg. %

TABLE III. GROUP B: EXAMPLES OF DNA-SE ACTIVITY MEASURED BY INCREASE OF OPTICAL DENSITY AT 2,600 Å

Purified DNA-se of pancreas	0.2 μg	0.202
Normal specimen	0.3 ml. CSF	No change
Meningitis specimen	0.3 ml. CSF	0.127
Paralytic polio specimen	0.3 ml. CSF	No change
Schizophrenia specimen	0.3 ml. CSF	0.014

RESULTS

The findings in about 200 individual cerebrospinal fluids are presented. Fifty samples from each of the following groups were described: normal, neurologically normal; meningitides; poliomyelitis; syphilis and miscellaneous psychoneurological diseases. Diagnosis was made by the hospital staff, cell count and protein determinations by the clinical laboratories. Table I shows the decrease of flow times, in seconds, Table II shows the increase of acid-soluble phosphorus of filtrate in milligrams per cent, and Table III the change of optical density of the system at 2,600 Å, after incubation. The diagram (Fig. 1) illustrates the relative viscosity changes of the system in selected examples.

Normal CSF's do not possess DNA-se in detectable amounts. Among non-neurological conditions a lobar pneumonia specimen showed the highest activity. However, the range and the average value of this group is the second lowest encountered during the whole study (Table I, group 1). Other techniques gave similar results (Table II).

The vast majority of the meningitis specimens exhibited the presence of DNA-se, the amount found depending upon etiology, clinical stage, and freshness of the fluid. Extremely active CSF's were found, but absence of DNA-se was also occasionally observed (Table I, group 2). The average was the highest in this group, although the range of activity was in second place in the whole study. One *Esch. coli* meningitis sample showed the strongest activity (Fig. 1). Bacterial culture was positive in this case, but in follow-up studies with five consecutive specimens in two months, the enzyme level remained still high, even when no growth appeared. Other methods confirmed these findings (Table II).

The various clinical forms were represented in the poliomyelitis group.

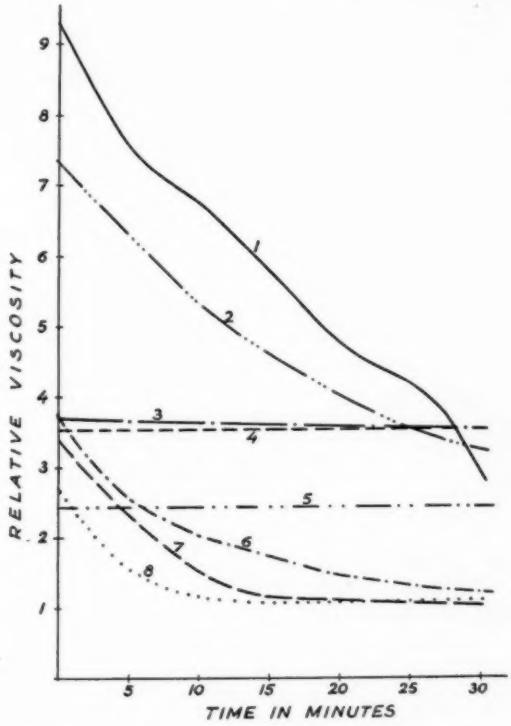

Fig. 1.—Drop of relative viscosity caused by DNA-se.
1, DNA substrate, 0.15% + 1 μg of DNA-se of pancreas.
2, DNA substrate, 0.15% + 0.3 ml. of a subdural hemorrhage sample.
3, DNA substrate, 0.1% + 0.3 ml. of a lobar pneumonia sample.
4, DNA substrate, 0.1% + 0.3 ml. of a paralytic polio sample.
5, DNA substrate, 0.1% + 0.3 ml. of a gastroenteritis sample.
6, DNA substrate, 0.1% + 0.3 ml. of an *Esch. coli* meningitis sample.
7, DNA substrate, 0.1% + 1 μg of purified DNA-se.
8, DNA substrate, 0.1% + 1 μg of purified DNA-se + 0.5 ml. of a paralytic polio sample.

About twice the number of samples were examined in preliminary assays. The range of activity and average were zero, the absence of depolymerase was 100 per cent (Table I, group 3). The lack of DNA-se was the most characteristic feature of fresh and frozen specimens of nonparalytic, paralytic,

bulbar, and encephalitic forms. CSF's of virus diseases, other than polio, behaved similarly. This subgroup was composed of choriomeningitis, infectious polyneuritis, mumps meningitis, mumps, and measles encephalitis. The miscellaneous neurological group was in second place with respect to average value (Table I, group 4). Syphilis, and especially neurosyphilis samples, contained moderately high enzyme levels in some instances. The CSF of a cured syphilis case caused marked decrease of viscosity. All the routine clinical examinations, bacteriological culture included, were negative; RNA-se and NA were demonstrated in the same fluid. Other cured syphilis samples did not exhibit any DNA-se activity. In many neurological and psychosis samples enzyme levels were demonstrated, without any apparent CSF changes in the great majority. Individually a subdural hemorrhage gave the most active specimens in the whole study (Fig. 1). The high enzyme level persisted for weeks, decreasing gradually, as revealed in follow-up studies. Schizophrenia, paranoia, genuine epilepsy, and tumor samples exhibited various degrees of depolymerase concentrations. There was a difference when the lumbar puncture was made in hyperkynetic or in quiet state. This series is being subjected to a special investigation.[13]

Illustrative examples are presented from the results obtained with various other techniques. In Table II, group A, the increase of acid-soluble phosphorus of the reaction mixture is compared with the action of known amount of DNA-se. The decrease of viscosity of the substrate is paralleled by increase of acid-soluble phosphorus in the system. The increasing solubility in acids is another sign of the depolymerization, measured by the method of Kunitz.[14] This technique was successfully used with CSF, as seen in Table III, group B. On the other hand the direct spectrophotometric method[14] was not found to be suitable, because of rapid and uncontrollable changes in the optical density of some CSF controls at 2,600 Å. Similarly the titrimetric method[2, 3, 14] was tried, but no reliable results could be obtained because of the strong buffering capacity of the CSF and of other ingredients.

Many assays were made for the investigation of the properties of the enzyme. No linearity was found between the increase of CSF volume added and the specific decrease of viscosity of substrate. Larger amounts than those routinely used were inhibitory. The effect of substrate concentration was found to be in agreement with that reported by Little and Butler.[17] Various pH ranges were assayed, the optimum being at, or around, 7. The type of buffer was not an important factor. Magnesium was the most potent activator, but manganese[18] also activated considerably. Citrate inhibits the CSF enzyme, as it does the DNA-se of pancreas.[18] Poliomyelitis specimens were assayed for inhibitor properties. Larger volumes (0.5 ml.) caused a decrease of the activity of dilute purified enzyme preparation (Fig. 1). Further studies are required to establish the specificity of this reaction. The notorious instability of DNA-se[14, 18] was observed during our assays also. Standing even at 4° C. caused its gradual decrease. Exposure to over 35° C. had a deleterious effect; five minutes at 90° C. caused its complete inactivation. Gel-

atin gave satisfactory protection against proteolytic enzymes and acted as stabilizer.[18] One freezing and thawing caused about 10 to 15 per cent loss in the enzyme; frequent repetition of this manipulation caused its complete denaturation. There was some difference between the specimens in this respect, depending probably upon protein content. Uncentrifuged and centrifuged CSF exhibited only slight differences if the cell count was not excessively high.

DISCUSSION

It is evident from the described results that the demonstration of active DNA-se in CSF's of some pathological conditions was successful. The activity is obviously comparable only to dilute solutions of purified, or crystalline, enzyme. The complexity of the CSF due to the presence of other enzymes and various substances adds to the difficulty of demonstrating DNA-se. CSF's derived from patients with meningitis were specially active. It is generally assumed[7, 8] that the CSF enzymes may originate in these conditions from the constituents of blood. An additional source of DNA-se could be the pathogenic microorganisms, some of which are known to be rich in this enzyme.[21] It is difficult to explain the activity in many neurological samples where the routine clinical laboratory tests gave negative results. The loss of neuronal material upon overstimulation in animals was described by Hydén.[6] It is quite possible that this factor plays a role in the release of nucleases into the CSF. Our findings showing occasionally the presence of NA and nucleases[11, 12, 13] tend to support this view. The nerve tissue is suggested by others[7, 8] as the site of origin of CSF enzymes.

The consistent absence of DNA-se in poliomyelitis specimens is significant, whereas RNA-se was of high level in the same specimens.[11, 13] The lack of the former is striking, since there are many signs of inflammatory reactions in the CSF's of this group. The sensitivity of DNA-se toward pH, proteolytical enzymes, and other factors[14, 16, 18] was confirmed during these studies, also. We feel, however, that this would not be a satisfactory explanation for the complete lack of this enzyme system in the large number of specimens investigated. The nuclei of the neurons are more rarely attacked in poliomyelitis,[5] compared with the almost universal involvement of the Nissl s bodies of the cytoplasm.[5] The former contain DNA and the latter PNA,[6] a substrate for DNA-se and for RNA-se, respectively. Our assays for some special inhibitory or toxic mechanism in poliomyelitis samples are not yet concluded. The dephosphorylation of NA[21] is a special problem in the CSF because nucleotidases are generally present. We are making a special study of these enzyme systems.

SUMMARY

About 200 specimens were examined for nucleodepolymerase. DNA-se is not as frequently demonstrable in the CSF as RNA-se. In normal or neurologically normal samples no DNA-se was found, as a rule, but a small number of nonneurological cases showed a very moderate degree of activity. The majority of meningitis, syphilis, epilepsy, hydrocephalus, and concussion specimens exhibited DNA-se activity. The absence of this enzyme in CSF's of all clinical forms of poliomyelitis was striking. The other important finding was the relatively high de-

polymerase level found in some neurological and psychoneurosis samples.

I wish to express my gratitude to Dr. D. T. Fraser, Head of the Department of Hygiene and Preventive Medicine, University of Toronto, for his advice and criticism; and to the staffs of the Toronto hospitals for the cerebrospinal fluid specimens kindly supplied. The present work was done with the technical assistance of Mrs. K. Vlossak. Miss C. Baky helped in the preliminary assays.

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ESOPHAGEAL PERFORATION COMPLICATING ACUTE INFLAMMATION OF THE BRAIN AND MENINGES

Report of Two Cases

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THERE have been several clinical reports over a number of years of damage to the gastrointestinal tract in patients with intracranial lesions.[1, 2] More recently, hemorrhage and ulceration in the stomach and esophagus have been observed in patients with bulbar poliomyelitis. The mechanism involved is not clearly understood but there is considerable evidence that damage to the hypothalamus is related to these gastrointestinal lesions.[2, 3] Sabin[4] found that the hypothalamus was always involved in experimental poliomyelitis, and recent work in human poliomyelitis suggests that lesions in the hypothalamus and erosions or hemorrhage in the intestinal tract are more common in bulbar poliomyelitis than was previously recognized.[5, 6, 7] In 1948 Heyde and Robinson[9] reported two cases of peptic ulceration accompanying bulbar poliomyelitis, and subsequently several similar reports have apeared.[6, 7, 8, 10]

Baker and associates[7] found inflammation in the hypothalamus in 85 per sent of a series of 115 cases of bulbar poliomyelitis. Sixteen patients had gastrointestinal hemorrhage. In these, the damage was most severe in the paraventricular and tuberal nuclei of the hypothalamus.

This paper is concerned with reporting and discussing two cases of esophageal perforation which appeared to be connected etiologically with coincident acute encephalomyelitis.

From the Pediatric Service, The Roosevelt Hospital.

CASE REPORTS

Case 1.—J. S., a 5-year-old boy, was admitted to the Roosevelt Hospital on Dec. 9, 1950, with a history of sore throat and intermittent fever of five days' duration. Shortly prior to admission he developed a stiff neck and had a fever of 101° to 102° F. On admission he appeared emaciated, dehydrated, and acutely ill, and his speech was slurred. On examination, apart from neck stiffness, there was injection of the pharynx, which was filled with yellowish mucoid secretions. There was hyperreflexia and the abdominal reflexes were absent on the left side. A pleocytosis in the spinal fluid with normal sugar, protein, and negative cultures confirmed the diagnosis of poliomyelitis. The pharynx was aspirated frequently because of the accumulation of large quantities of mucoid secretions. On the second hospital day the neck stiffness increased and the patient became comatose. All deep tendon reflexes were absent at this time and weakness of the left palatine fold was noticed. It became difficult to free the airway of secretions, and respirations became rapid and shallow, with cyanosis of the mucous membranes. Finally, tracheal suction was carried out through a laryngoscope by an anesthetist. In the evening of the second hospital day the patient was placed in a body respirator, as the thoracic respirations had almost ceased, with prompt improvement in color. However, the temperature, which had fluctuated between 101° and 104° F., rose to 108° F. On the

following day, although the temperature had dropped to 103° F., the patient expired.

Autopsy Findings.—The brain herniated through the opening made by incision of the dura. The convolutions were flattened over the cerebral hemispheres and there was a compression ring at the base. The basal part of the brain (Fig. 1) and the medullary region were hyperemic but to a lesser extent than the cervical region of the cord. The dura of the spinal cord was diffusely hyperemic and the pia was injected, particularly in the lumbar region. There was diffuse inflammatory reaction of the gray matter, most marked in the lumbar region but also in the thoracic and cervical areas of the cord. A small amount of coffee-ground material was present in the stomach. The lower third of the esophagus was softened and contained a perforation measuring 12 mm. in the long diameter. The softened area involved about 2 cm. of the length and was discolored a dirty greenish gray. The left pleural cavity contained a few cubic centimeters of coffee-ground material, and the left upper lobe was completely collapsed. The pleura along the lower third of the esophagus showed a dark grayish discoloration. The tracheal mucosa was reddened and the bronchi contained brownish material similar to that seen in the esophagus.

On microscopic examination there were multiple pericapillary hemorrhages, perivascular infiltration with lymphocytes, and a few neutrophils in the medulla and spinal cord. The cord showed chromatolysis of ganglion cells in the horns and a mild degree of neuronophagia. There was necrosis of the esophageal mucosa with mild to moderate infiltration with inflammatory cells, mostly neutrophils. The adrenals were normal.

Comment.—This case appears similar to those already reported. Unfortunately, serial sections of the hypothalamus were not made.

It seems possible that in some cases of acute meningitis involving the base of the brain there may be an extension of the inflammatory process into the hypothalamus. Cushing[1] quotes Blackfan as noting gastrointestinal ulceration with perforation associated with acute meningitis, and Vonderahe[11] has reported a case of tuberculous meningitis in which the tuber cinereum was invaded by the infectious process; here there was ulceration of the terminal portion of the ileum.

CASE 2.—S. S., a 6-year-old boy, was admitted to the Roosevelt Hospital on Feb. 26, 1951, with a history of vomiting, drowsiness, and occipital headache of two weeks' duration. His speech was slurred and he had a slight dry cough. He had been delirious and finally unconscious prior to admission. Over a period of several months he had lived in close contact with his mother who was suffering from active pulmonary tuberculosis. On admission the child appeared undernourished and was acutely and chronically ill. The temperature was 104° F. He was stuporous and responded only to painful stimula, occasionally moving his right hand. The pupils were dilated and did not react to light. Corneal reflexes were diminished. The fundi were normal. The neck was stiff and deep tendon reflexes were hyperactive on the right side. Babinski's sign was present bilaterally and both Brudzinski's and Kernig's signs were positive. Abdominal reflexes were absent, and the whole body was spastic with the exception of the left arm. Examination of the lungs was negative but the chest x-ray showed increased markings in the left infraclavicular region. The diagnosis of tuberculous meningitis was confirmed by many positive cultures for tubercle bacilli from both gastric washings and spinal fluid, a low cerebrospinal fluid sugar, and a positive old tuber-

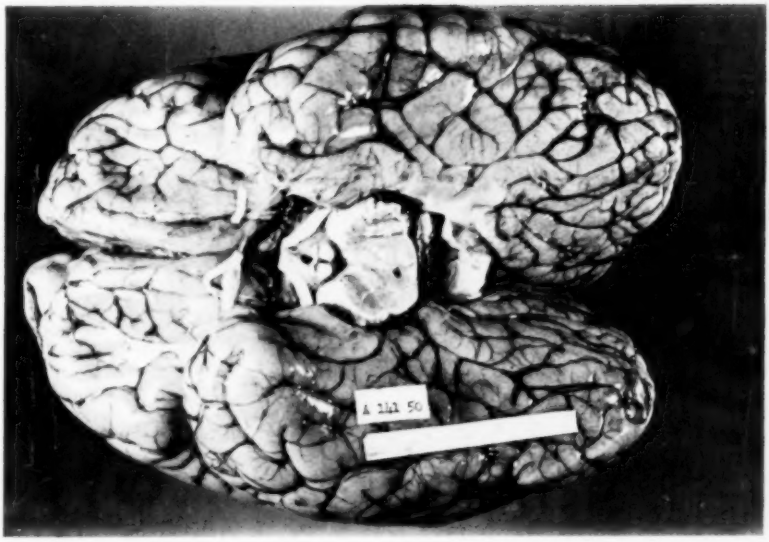

Fig. 1.—Base of the brain showing hyperemia. Case 1.

Fig. 2.—Lesion on the posterior surface of the lesser curvature. Case 2.

culin test to a dilution of 1:100. By March 2, 1951, the child improved following treatment with streptomycin and Promizole; he answered simple questions and took fluid by mouth. However, on March 7, he became extremely lethargic and by March 17, had developed tonic neck patterns and marked tremor of the right arm. Burr holes were made March 19, as it was felt a block in the cerebrospinal fluid pathway was developing. Following this operation the temperature, which had ranged between 100° and 103° F., rose to 105° F. and could not be controlled by sponging. The child died on March 20, 1951. This patient had received tracheal suction and some gastric feedings, the last of these on the day before he died. All intubations were personally performed with care by the author.

Autopsy Findings.—There was a pressure ring around the foramen magnum, and over the cerebral hemispheres the convolutions were flattened to a considerable degree. There was tuberculous basilar meningitis with thick gray exudate involving the brain stem, particularly the pons. The cord was hyperemic. A tear of the esophagus and upper portion of the stomach was seen, with leakage of gastric contents into the surrounding tissue. This tear was situated about one inch above the esophageal hiatus, extending toward the right of the esophagus, and was about 2 cm. in length. The opening was elongated and the wall immediately around it appeared normal in consistency. Some hyperemia was present. There were some autolytic changes on the surface of the esophagus. There was a laceration of the stomach (Fig. 2) 2 cm. from the cardia on the posterior surface of the lesser curvature, measuring 1:5 cm. in length. The serosal surface of the stomach showed autolytic changes. Brownish fluid was present in both pleural cavities, and on the left the lining was hyperemic over the diaphragmatic and lower parietal surfaces. The pleural and mediastinal tissues in the area adjacent to the esophageal perforation were discolored brown from esophageal contents. The lower lobes of both lungs showed patchy reddish discoloration over the medial aspects, and there was hilar lymphadenopathy. The adrenals appeared normal. Microscopically there was miliary tuberculosis of the liver and spleen and tuberculous involvement of the meninges. Microscopic examination of the esophagus was not made.

Comment.—Vomiting was a prominent symptom in this case and it seems possible that the mechanism leading to rupture of the stomach and esophagus was similar to that seen in spontaneous perforation of the esophagus. In the latter condition it has been suggested that a sudden increase in intra-abdominal pressure usually due to vomiting leads to rupture often in the left lower extremity of the esophagus, which is the weakest part.[12] Barrett[13] recommends distending the gut with water at autopsy before opening it if spontaneous perforation is suspected. The esophagus may look as if cut by a knife, for the incision ordinarily made may pass through the lesion, which may be missed completely.

DISCUSSION

French and associates[2] reviewed clinical cases in the literature where brain damage was associated with gastrointestinal lesions. They found that the diencephalon was involved in half the cases, and in many of the remainder the lesions were so situated that interference with hypothalamic connective pathways resulted. Lesions involving the frontal area of the brain or the brain stem have also resulted in gastrointestinal symptoms or ulceration,[14, 15] and it is believed that

vagal irritation may lead to ulceration and other intestinal lesions.[15]

Supporting clinical observations, there is considerable experimental evidence connecting hypothalamic stimulation or injury with gastrointestinal lesions. There is strong support for the existence of a sympathetic center regulating gastrointestinal activity located in the lateral hypothalamus.[16] Stimulation of the posterior hypothalamus and frontal cortex will also evoke sympathetic responses.[2, 17] Some observers have recorded motor responses in the stomach and intestine with increased flow and acidity of gastric juice following stimulation more anteriorly in the supraoptic and preoptic areas of the anterior hypothalamus.[2, 16] Sheehan[3] carefully summarized the experimental data in 1939 and concluded that hypothalamic injury was followed by mucosal hemorrhage and erosion in one-third of all experiments. The site of injury was primarily the tuberal region[7, 16] and to a lesser extent the supraoptic region. Hypothalamic lesions were followed by gastrointestinal changes much more frequently than lesions placed elsewhere in the central nervous system.[16] Finally, gastrointestinal changes have been observed in animals following experimental lesions in the frontal cortex, midbrain, pons, and also following transections of the spinal cord.[16, 17]

The part played by stress and hormones in the development of gastrointestinal ulceration and hemorrhage is incompletely understood and is reported at length elsewhere.[18, 19, 20] Such relationship as may exist between hypothalamic damage and stress is still speculative. Acute emotional stress is believed to be transmitted to the intestinal tract by way of the vagus, and systemic stress is thought to be expressed through the hypothalamus and relayed thence to the vagal centers. However, a hormonal mechanism is apparently also involved in gastrointestinal ulceration.[21, 22] It seems that chronic stress, either emotional or physical, is transmitted to the stomach by a hormonal mechanism mediated through the adrenal glands. This may induce gastrointestinal ulceration through the hypothalamic-pituitary-gastric pathway.[21] The hypothesis, however, is not completely satisfactory, since hypophysectomy and adrenalectomy usually aggravate gastrointestinal lesions.

The role of trauma as a cause of intestinal perforation must also be considered, as intubation is often justified for suction and gavage in the type of case reported. It was felt that trauma was definitely not a factor in the first case reported and was unlikely in the second, and this was also the opinion of most of the authors whose reports have been mentioned. Distention, however, has been a complication in some cases.[7] Some authors feel that regurgitation of gastric contents with peptic digestion of the esophageal mucosa may be an important factor in producing esophageal lesions, particularly if the patient is recumbent or in the Trendelenburg position. Erskine and associates[10] noted that in both their cases ulceration was in the posterolateral esophagus. Both hemidiaphragms were paralyzed in each case, which may have facilitated regurgitation. They suggest that recurrent acid reflux could produce trauma when a respirator is being used.

In conclusion, it seems important to recognize that in bulbar poliomyelitis gastrointestinal lesions may be a possible complication. In this disease or in other severe infections involving the diencephalon, the early recognition of intestinal hemorrhage, distention, or ulceration may be an important factor in reducing the mortality rate.

SUMMARY

Two cases are reported in which esophageal perforation occurred, associated with acute inflammation of the brain and meninges. Each patient was severely ill for some time before death, and both stress and hypothalamic damage seem likely contributory factors. It seems possible that lesions of the gastrointestinal tract can occur in any severe infection if there is sufficient damage to the diencephalon.

I wish to thank Drs. Alexander T. Martin, Edmund N. Joyner, III, and Walter Brandes for permission to publish these cases.

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CIRCULATION TIME IN THE NEWBORN INFANT, USING THE FLUORESCEIN DYE METHOD

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A RELIABLE method for determining circulation time is a necessary part of the diagnostic study of some cardiac problems. Elaborate cardiac diagnostic equipment is not readily available to all clinicians.

The various methods which depend on a taste endpoint determination such as saccharin, Decholin, and calcium gluconate are not suitable for use with small infants. Fluorescein is a relatively nontoxic preparation which fluoresces under an ultraviolet light. It may be given intravenously, and its appearance measured accurately by a Woods filter light, either on the lips or the conjunctiva.

Lange and Boyd[1] used fluorescein to determine adequacy of circulation in medical and surgical problems. The medical indications for determining circulation time are congenital heart problems, cardiac failure, hypothyroidism, and hyperthyroidism. The surgical indications are the evaluation of the vitality of incarcerated bowel in intestinal obstruction problems, and the determinations of the site for amputation in peripheral vascular disease or diabetic gangrene.

Gasul and associates[2] timed the interval between the injection of the dye and its recognition in a series of thirty-two congenital heart problems and twenty-five rheumatic heart disease cases. They concluded that the circulation time is shortened in tetralogy of Fallot, tricuspid atresia with an intra-auricular septal defect, and transposition of the great vessels. There were no abdominal changes in the rheumatic heart cases if decompensation was not present.

Slobody and co-workers[3] reported a study of circulation time using the umbilical vein immediately after birth. The mean time was 4.8 ± 0.6 seconds.

Lesser and associates[4] reported a series of fifty-five newborn infants, using the wrist-to-conjunctiva technique. The average time was 10.2 ± 4.2 seconds.

Due to the lack of other reports giving values for the newborn period, we endeavored to repeat the work by Lesser and associates[4] from the Childrens Hospital in Detroit.

METHOD OF STUDY

In this study we used Fluorescite. The intervals from the beginning of the injection in a wrist vein to the appearance of the dye in the conjunctival membrane were measured by a stop watch. The amount of dye used was 0.07 c.c. per pound of body weight. A No. 24 needle was used in all determinations to standardize the rate of ejection of dye from the syringe.

The subjects were normal newborn infants delivered at the University of Nebraska Hospital. The age ranged from 1 to 42 days. There were thirty infants in the group

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TABLE I

CASE NO.	AGE IN DAYS	WEIGHT (LB. OZ.)	C.C. OF DYE INJECTED	CIRCULATION TIME IN SECONDS	D*	D²†
1	N. B.	7 8	0.5	6.5	1.3	1.7
2	N. B.	6 8	0.4	5.5	2.3	5.3
3	N. B.	7 12	0.5	5.5	2.3	5.3
4	N. B.	5 4¾	0.3	5.0	2.8	7.8
5	8	6 6½	0.5	6.0	1.8	3.2
6	5	6 4¾	0.4	8.5	0.7	4.9
7	12	5 9¾	0.4	8.0	0.2	.04
8	3	5 11½	0.4	7.0	0.8	.6
9	33 premature	5	0.4	7.5	0.3	.09
10	7	8 15	0.6	8.0	0.2	.04
11	6	5 2¾	0.4	7.0	0.8	.6
12	3	8 3½	0.6	7.5	0.3	.09
13	10	7 13	0.5	9.0	1.2	1.4
14	1	7 6¾	0.5	10.0	2.2	4.8
15	7	6 9	0.5	7.5	0.3	.09
16	4	6 13	0.5	8.0	0.2	.04
17	2	6 8	0.5	10.0	2.2	4.8
18	4	7 4	0.5	8.0	0.2	.04
19	42 premature	5 10	0.4	9.0	1.2	1.4
20	N. B.	7 14	0.5	7.5	0.3	.09
21	5	7 6	0.5	9.0	1.2	1.4
22	6	6 5	0.5	6.0	1.8	3.2
23	6	7 4	0.5	10.0	2.2	4.8
24	N. B.	7	0.5	7.0	0.8	0.6
25	N. B.	7	0.5	9.0	1.2	1.4
26	8	7	0.5	8.0	0.2	.04
27	5	11	0.8	9.0	1.2	1.4
28	10	7 5	8.5	8.0	0.2	.04
29	3	6 4	0.5	8.0	0.2	.04
30	6	7 5	0.5	9.0	1.2	1.4

*Difference between the mean and observation.
†Difference between the mean and observation squared.

TABLE II

CASE NO.	AGE IN MONTHS	WEIGHT (LB. OZ.)	C.C. OF DYE INJECTED	CIRCULATION TIME IN SECONDS
1	8	17	1.2	8.9
2	2½	9 11½	0.7	12
3	2	10	0.7	10
4	3	12	0.8	8
5	2	11 4	0.8	13
6	4	14	1	7.6
7	8	16½	1.2	8
8	11	17	1.2	12
9	12	19	1.3	11
10	2	9	0.6	9.0
11	6	12	0.8 (hydrocephalus)	9.0
12	5		0.9 (pneumonitis plus URI)	9.0

(Table I). Determinations also are included from a group of 12 infants ranging from 2 to 12 months of age (Table II).

DISCUSSION

A simple technique to determine circulation time in small infants is needed. Most methods are inadequate for use in the majority of the hospitals. The fluorescein method surmounts these inadequacies. The lack of published figures in significant series prompted this study. This method can be used in all age groups without difficulty. The technique is simple and relatively harmless. The mean circulation time in this study is seconds 7.8 ± 1.4 seconds.*

SUMMARY

1. The technique of the fluorescein circulation time by the wrist-to-eye method is described.

2. A series of thirty newborn infants is reported. The average circulation time in this group is 7.8 ± 1.4 seconds.

3. A series of twelve infants from 2 to 12 months is reported. The average circulation time in this group is 10 ± seconds. The latter group is not large enough to be statistically significant.

*The statistical analysis was done by Dr. J. L. Gedgoud, Associate Professor of Pediatrics, University of Nebraska, College of Medicine.

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COMMON ERRORS IN INFANT FEEDING

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IT SEEMS inevitable that the popularization of any new concept in science should initiate a swing far beyond the original intention. When Aldrich and associates[1] at the Mayo Clinic pointed out the need to individualize infant feeding, the "demand" concept was born. They emphasized that rigidity in infant feeding—the idea that a fixed three- or four-hour interval— and exactly 3 or 4 ounces—and exactly five to seven feedings per twenty-four hours—was unwise, and that the average baby could tolerate from five to nine feedings per twenty-four-hour period, with variations from 2 to 6 ounces at each feeding. This concept agreed well with the experience of most practicing pediatricians, and was part of the general swing to a permissive type of discipline from the old-fashioned, clock-watching routine. Since then, so many excesses have been committed in the name of the "demand" concept, the latest being "a streamlined plan of infant feeding," that it seems time to re-examine our present status.

At the obstetrical hospital, the newborn infant is given a fixed formula, affording from 16 to 20 calories per ounce, and fed on strict schedule until his discharge. The usual directions "feed the child whenever he is hungry, as little or as much as he pleases," are then given to the mother. The parents, unable to differentiate a hunger cry from one produced by gastrointestinal pain, spasms, air swallowing, or any of the many causes of whining in the neonatal period, feed the child every time he cries. This has resulted in a substantial number of cases of a new syndrome—"acute demanditis." One horrible example is the 10-day-old infant recently seen who had been fed, by actual count, twenty-three times in a twenty-four-hour period, with resultant vomiting and diarrhea.

Such *frequency of feeding* may be possible with the monkey mother or rarely with the human breast, but never cow's milk formulas. The reason for this difference is the nature of the lactating breast. A nursing mother can often feed her baby breast milk at 20 calories to the ounce every hour or two, with no bad effect. Emptying a breast requires active sucking on the child's part, and often so much energy that he becomes tired, unless he is really hungry. In contrast, the nipple on a bottle flows so easily that overfeeding is very easy. This is the explanation of the almost invariable refusal of babies to take the breast again after a temporary weaning to the bottle. Why should they work?

Here it may be worth while to review what the extremists in "demand feeding" have led us to. A sociological study[2] reports, "They (the writers in the field of infant care)

have often reflected the changing patterns of thought in personality formation." Bakwin,[3] certainly a psychiatrically oriented physician, found it necessary to warn "the physician will need to discriminate between those mothers who are ready for self-regulation and those who need the extra support which they get from more or less precise prescriptions." Rothman[4] recently reviewed Bakwin's list of the adverse effects of "demand feeding" as, first, parents and nurses unable to differentiate hungry cry from other causes of crying; second, child upsets entire household by irregularity in feeding; third, it is the first step in a pattern of extréme permissiveness and no discipline, and fourth it increases anxiety in certain types of mothers, especially the "orderly and executive" type. All of these difficulties, and more, have been noted in my own practice, and for this reason, a plea is made that a commonsense motto such as "Demand Feeding Within Reason" be adopted. This might be explained as allowing the baby to feed at three- to five-hour intervals as little or as much as he pleases of a formula which he will finish (thus allowing for the retention of the all-important appetite), and which gives him a satisfactory gain of perhaps 5 to 10 ounces a week. Even the Freudian school now admits that discipline is not a dirty word, and that parents are people. Perhaps such a pragmatic viewpoint of moderation can now prevail.

The extensive growth of *ready-made formulas* in recent years has posed a new problem for the pediatrician. Such preparations as Similac, Bremil, Dryco, and Lactum need merely the addition of water to be a complete formula, "thus giving uniform composition and unequalled convenience." Actually what should concern us is whether such a "fixed" or "ready-made" formula, containing a definite proportion of one particular kind of sugar to the fat and protein, is wise for the general feeding of newborn infants. The convenience is merely that the mother does not find it necessary to add a number of tablespoons of a sugar to the measured quantities of milk and water. My objections are first, that we are not able easily to vary the percentage of sugar in the fixed formula. Children differ in their tolerance for sugars, and most pediatricians learn to be elastic in the quantity added. For bowel control, the older pediatrician omitted the sugar for diarrhea, and increased or varied the sugar for constipation. Second, a small but growing percentage of infants seem unable to tolerate the disaccharides and complex polysaccharides, and require a change to a monosaccharide such as dextrose or banana powder. Third, such formulas easily lead to overfeeding. Thus, while the manufacturers of Lactum distribute "condensed feeding tables" in which they give a typical formula for a 6 to 7 pound newborn, as Lactum 8 ounces to water 13 ounces, the tendency in many hospital nurseries has been to feed a higher concentration, a 1:1 mixture. This results in a formula supplying 20 calories to the ounce, the equivalent of breast milk or whole cow's milk. In contrast, our usual 1:2 dilution of evaporated milk formulas runs 16 calories to the ounce and the 1:1 whole cow's milk formulas approximately 12 calories to the ounce. The ob-

jection to feeding a concentrated formula to newborn infants is first, that anorexia is frequent, and, second, "demand" or not, when the baby finishes much less than the hospital formula, the mother (and nurse's!) almost invariable procedure is to force the last ounce down the unwilling mouth. This is not theory on my part; since a large New York City hospital recently adopted a fixed formula, I have seen a dozen or more infants recently discharged from its newborn service with feeding difficulties produced in this way. Jackson[5] had noted that during the early days of feeding, the smaller babies developed loose stools unless the formula was diluted in the proportion of 1 part to 2 or 3 of water. Frost and Jackson,[6] in a widely quoted study, did not start at birth "as the smaller infants are more likely to need adjustments of formula to meet their individual needs." A recent comparison of fresh milk, evaporated milk, and Lactum 1:1 formulas by Hatfield and associates[7] found the 1:1 concentration well within the tolerance of the healthy newborn and very young infant. The work on Lactum is based on study of thirty-nine neonatal infants and about sixteen infants from 1 to 8 weeks of age, surely a small number from which to draw comparisons. My own experience, based on much larger numbers, would lead me to doubt the ability of most newborn infants to cope with these fixed formulas giving 20 calories to the ounce, and to warn against feeding difficulties, often severe.

Another recent innovation is *feeding without added* carbohydrate, i.e., evaporated or whole milk formula with water only added. Harris[8] found essentially the same gain, the same amount of formula taken, fewer cases of constipation, and perhaps somewhat less colic for infants fed formula without added carbohydrate. Whether this one study should lead us to overthrow the old conception that the consistency of the stools can be influenced by the carbohydrate is doubtful. But a recent work by Pratt,[9] contrasting infants fed with and without added carbohydrate, noted that such a procedure led to an intake of about 40 per cent more protein and minerals with an increased renal solute load of 85 per cent, which definitely decreased the margin of safety agaisnt dehydration. In both of these studies, the milk formulas fed ranged about 20 calories per ounce, i.e., definitely more concentrated than our experience has previously considered. It seems probable that Pratt's study will dispose of the feeding without added carbohydrate innovation.

At this point, *underfeeding* as a cause of difficulties in the newborn period must be discussed. In England, Vining[10] attributes vomiting, screaming, colic, abnormal stools, and failure to gain to underfeeding, Wicks[11] discusses the "morbid fear of overfeeding" in the early weeks, and Wood,[12] in a study of forty-six cases of vomiting, found six due to underfeeding. Since the British use much more breast feeding than we do, and powdered milk formulas almost exclusively, their experience does not seem pertinent to us. However, in a recent symposium on underfeeding,[13] all the authors but Bret Ratner agree on underfeeding as the main cause of difficulty in the neonatal period. No

really comprehensive study has been done on the incidence of feeding difficulties in infants fed diluted whole milk formulas at 12 calories to the ounce, diluted evaporated milk formulas at 16 calories to the ounce, or the 1:1 fixed formulas at 20 calories to the ounce. While it seems possible that the very dilute whole milk formulas of a generation ago could be associated with underfeeding, it does not seem likely that the more concentrated milk formulas can be charged with this fault.

Here the question of "colic" comes in. Watson[14] feels that when colic is the chief complaint, if the formula is good, it should not be changed, but the technique of feeding should be revised. Too frequent belchings interrupt the feeding, producing crying and thus more nervous tension and colic. Air swallowing from crying, faulty nursing, and sucking on an empty bottle may be other causes. Gottschalk,[15] a physician working as a "baby nurse," reports a vicious circle of much crying, leading to exhaustion, so that little food is consumed, and hunger starts at irregular intervals, with more disturbance of sleep and crying. She recommended feeding in bed with the head propped up on diapers, meticulous care of the size of the holes in the nipples, holding at 45 degrees to belch, etc. The subject of colic is far more complex than generally realized, as shown by the experience of Horton and co-workers[16] who worked in a premature nursery with highly trained nurses, thoroughly understanding "crying, the nature of which varied from infant to infant when it signified hunger." The complexity is shown by a psychiatric study by Stewart and associates[17] of excessive infant crying, which they characterized as a response to tension arising "internally from unsatisfied needs or from inappropriate external stimulation."

Some of the *varieties of colic* may be worth detailing. Rarely do I see *hunger colic* any more, but certainly all of us will test this possibility by increasing food to the point of tolerance. More frequent is *overfeeding colic* where a simple reduction from 75 to 45 calories per pound and then a gradual increase transforms the baby into a relatively happy infant. Very common is what we called *hypertonic colic*—the tense, hypertonic infant of a primipara, often the product of a difficult labor, whose rigidity gradually disappears in the course of a month or two, but who often vomits from pylorospasm. In these, small doses of phenobarbital frequently evoke gratifying relief. The *nervous tension evening colic* is also common—the infant who selects 6 P.M. to midnight as his crying jag to demonstrate the tired businessman reaction. Here much outdoors and a cold bedroom, with changes in bath and feeding routine, are all that is necessary. The so-called *rectal colic*, popularized years ago by the introduction of graduated rectal dilators, has never seemed convincing and, I hope, has been given the *coup de grâce* by the Mayo Clinic demonstration[18] that these infants do *not* have a tight rectal sphincter or rectal contraction rings. The *allergic colic* diagnosis has been misused of late. Rarely does this occur in a child whose family history does not demonstrate major allergic episodes, and it is usually possible to demonstrate eosinophilia either in the mucus from vomitus or in the mucus from the

stool. A trial of a synthetic formula free from cow's milk may then be indicated, and will be discussed in the section on "failure to gain." But there are still too many *idiopathic colic* reactions. Whether the use of a pacifier[19] does more harm by allowing sucking but encouraging air swallowing is a moot point; a more diluted formula would afford more chance for sucking without air swallowing. In these cases, careful attention to technique of feeding, upright or in bed, belching frequently or not at all, feeding on demand or less frequently, will often prove helpful. A roentgenologist friend,[20] whose infant son suffered from intractable colic, showed me x-rays demonstrating large volumes of gas trapped in the stomach and small intestine, relieved only by changes of posture, hot stupes to the abdomen, and occasional enemas. So few of this group have been thoroughly studied in a hospital that none of us can speak with authority. However, usually repetition of the magic "three-month" period will get us off the hook.

Gradual increase of caloric intake in the young infant seems to be another lost art. We were taught to increase perhaps 5 calories per pound per day, if well tolerated. As a consequence, at feeding supervision visits we increased the formula constituents—one at a time—½ ounce of evaporated or 1 ounce whole milk each day, alternating with ½ tablespoonful of sugar increase. Thus we wrote a number of slowly increasing formulas rather than one formula for the next month, with a large jump in both milk and sugar. Surely ours, while more time-consuming, was the more physiologic and safer practice.

Failure to gain in early infancy is no longer a frequent occurrence. Here, in my experience, where the child is ingesting sufficient calories, simple office tests on stools prove valuable. A demonstration of eosinophils in the mucus collected from the stool may point to allergy, a failure to show trypsin in a normal dilution by the gelatin film test may be the clue for a diagnosis of cystic fibrosis, and demonstration of undigested starch and fat may force a diagnosis of infantile steatorrhea or celiac disease. It cannot be too strongly emphasized that diarrhea is not necessary for a diagnosis for any of these syndromes (i.e., allergy, cystic fibrosis, infantile steatorrhea, or celiac disease) but merely an alteration in the normal composition of the stools. It is my feeling that excessive starch in the stools can be found in the siblings of many cases of celiac disease, and that treatment of such siblings with a so-called celiac diet will usually prevent the emergence of the full-blown disease.

Later in infancy and childhood, failure to gain is commonly due to the so-called "milk anorexia." The runabout, from 1 to 3 or 4 years of age, often too impatient to bother with solid foods, lives on milk only, though some part of this is surely satisfaction of oral eroticism by much nipple sucking. These children, no matter how much milk they ingest, seem to do poorly. Often, a milkless diet for several weeks is necessary to break this vicious cycle. In this age group, too, routine stool tests are useful. Examination of stool by the Dutton stain should then be added, since demonstration of many polynuclear cells may give evidence of a subclini-

eal dysentery or amebiasis, while demonstration of eosinophils may point to loss of calories through allergic reactions of the gastrointestinal tract.

Harm from *early introduction of solids* may be discussed at this point. Years ago, few children received solids before 5 or 6 months of age, but this has received progressive speeding up, until several hospitals have experimented with egg yolk at 2 weeks of age, and many more with cereal at 4 weeks of age. Glaser[21] and other allergists have emphasized the harm such early introduction of potent allergens does in potentially allergic infants. Dicke and coworkers[22] and Anderson's group[29] have adduced evidence pointing to the fact that instances of cereal intolerance in celiac patients are attributable to hypersensitivity to the protein of the cereal rather than to its starch content. This and di Sant'Agnese's work[23] may explain the marked rise in the incidence of celiac disease on the basis of early feeding of wheat. The demonstration that amylase is first demonstrable in the human infant at 3 months of age[24, 28] gives us some notion of when it may be safe to start starchy solid foods. Watson[25] explains that in urban areas this question of early introduction of foods is really a popularity contest between pediatricians, and needs stern measures for its repression.

Harm from abnormal formulas, long-continued. Glaser,[26] although generally so conservative, finds that infants who are milk sensitive do well on soybean milk. Watson[27] notes the "strong likelihood of hypoproteinemia or other disturbances of nutrition." Milk has proved so basic that only long-term balance studies of soybean milk, meat milk, whale milk, etc., could possibly show whether these can seriously be considered as long-term substitutes to be used in "potentially allergic" babies. More conservative it would seem to employ them for short periods, and then to produce a very slow, careful, oral desensitization to milk as was the practice in a previous generation. *Orange juice* can be omitted in the presence of synthetic vitamin C, as well as natural vitamins for fish sensitivities, etc.

In conclusion, careful observation and testing of the effect of each new formula and each new food on the child as an individual are likely to be far more rewarding than any catchword phrases such as "streamlined plans" or "balanced conceptions" of infant feeding.

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THE 2 A.M. FEEDING

"In those first weeks and months of her," writes Donald Culross Peattie* about his little daughter, "we had one regular appointment, she and I; this was at two o'clock in the morning, the time for a necessary extra feeding. When the alarm clock woke me I would smother it; then in the dark I went to gather up the light warm burden and bring it to her mother, who was still sleeping the thirsty sleep of one who must repair the cost of a whole life. While the child nursed and my tired wife drowsed, I sat by the bed and kept watch of them for twenty dark and silent minutes. Altogether those minutes made a piece of life I shall not lose. It was summer then; I was not cold, but I had to fight for vigilance against the ache to sleep. I used to watch the stars, through the scanty pines whose boughs and needles broke up the constellations. There, beyond the sheltering blanket of our atmosphere, stretched coldness indeed, the icy black of outer space. And here was I, in the snuggest of Nature's many mansions; here were the three of us together in the night. Three, you know, is the number that will just enclose an area, just balance anything that can stand alone."

*Peattie, D. C.: The Road of a Naturalist, Boston, 1941, Houghton Mifflin Co., p. 197.

REGARDING THE TRANSITION OF A CASE OF THE "ABT-LETTERER-SIWE" DISEASE TO "LIPOID GRANULOMATOSIS"

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RECENTLY we had the opportunity of studying in our clinic the transition of a case of the Abt-Letterer-Siwe disease to lipoid granulomatosis.

It is an accepted fact that by reticuloendotheliosis is meant a rare syndrome which is especially seen during childhood and which presents various clinical forms. The reticuloendotheliosis group includes: (1) the Hand-Schüller-Christian disease, (2) the Abt-Letterer-Siwe disease, and (3) eosinophilic granuloma. The first of these to be known is the Hand-Schüller-Christian disease which later was divided into essential xanthochromatosis of the normocholesterolemic type and lipoid granulomatosis.[1]

The Abt-Letterer-Siwe disease is a nonlipoidic reticuloendotheliosis which was first believed to be a disease sui generis. Siwe[2] declared that some forms of nonlipoidic reticuloendotheliosis could be differentiated through their etiology and named this group infectious reticuloendotheliosis (1933). Later, Glanzmann,[3] Wallgren, and Letterer supported this idea. Wallgren accepted a number of reported cases to be infectious in nature. The eosinophilic granuloma was named solitary bone granuloma by Otani and Ehrlich,[4] and eosinophilic granuloma by Jaffe and Lichtenstein.[5] It has been put forth that these syndromes, which seemed to be separate diseases, were in reality only various manifestations of an unknown etiology. In 1940, Glanzmann published a case of the Abt-Letterer-Siwe disease, some symptoms of which resembled the Hand-Schüller-Christian disease. Wallgren[6] published a similar case and concluded that there was an overlapping of boundaries between these two diseases. Love and Faschena[21] presented some cases which would be between an eosinophilic granuloma and the Hand-Schüller-Christian disease.

The idea that eosinophlic granuloma constitutes the primary stage of the Abt-Letterer-Siwe disease has not been realized.[7] Following these early first observations, the number of reports on intermediary cases has increased. However, only part of these reported cases proved to be correctly diagnosed when verified post mortem. Jaffe and Lichtenstein have shown the close relationship existing between the three forms, and Thannhauser went even further and proposed common nomenclature for all three (eosinophilic xanthomatosis granuloma).

Later, however, Jaffe and Lichtenstein, considering the clinical differences, preferred to regard eosinophilic granuloma as a separate clinical entity, in spite of the fact that all three types of the disease may have a common etiology.

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CASE REPORT

D. N. (Prot. No. 1344), a 20-month-old male, was admitted to the clinic on Nov. 26, 1953, with symptoms of polydipsia, polyuria, swelling of the abdomen, and otorrhea. The parents, father 23, mother 21 years of age, are healthy. There were no hereditary diseases. The patient weighed 4,500 grams at birth. He was the second child of the parents.

The infant was breast fed for fourteen months with no regular feeding hours; he was recently changed to adult food. He had his first tooth when 9 months, walked when 12 months of age. No symptoms of illness were present until 9 months of age, when otorrhea developed, which disappeared temporarily with penicillin therapy. It recurred one month later, and the discharge persisted. The patient had measles when 14 months and whooping cough when 18 months of age.

Three months prior to admittance to the clinic, the mother observed a tumefaction over the right ear, probably related to bone tissue. After a period of time the tumefaction disappeared.

One month prior to admittance, the child started to drink large amounts of water and pass proportionately large amounts of urine. The child who, up to that time, reported when he had to urinate, started not to do so. Enuresis also occurred. At the same date, slight swelling of the eyelids started, followed by swelling of the abdomen and small eruptions on the skin. The patient was admitted to the Izmir Children's Hospital on Nov. 18, 1953, with a diagnosis of diabetes insipidus. Injections of neurohypophysis extract caused a rise in temperature of 39° to 40° C. The patient was transferred to our clinic after fourteen days at the above-mentioned hospital.

Upon physical examination the general state was found to be fair. Weight was 8.5 kilograms. There was decrease in turgor, muscle tonus, and subcutaneous fat. The ear was sensitive to pressure. There was swelling of the eyelids and edema of the feet. The skin was pale; ulcers 0.5 cm. in diameter and of a yellowish appearance were present on both cheeks. These appeared, it was stated, following a minor trauma some time before entering the hospital in Izmir. These lesions continued for two and a half months after admittance to our clinic.

Fig. 1.

Petechiae were present on the upper thorax. The tongue and lips were dry. Sixteen teeth were present with caries on the upper incisors. Tonsils were hypertrophic. No other pathologic changes were in the mouth region.

The liver exceeded the costal margin by 4 fingerbreadths. Its relative dullness started at the sixth intercostal space. The spleen exceeded the costal margin by 2 fingerbreadths;

Fig. 2.

Fig. 3.

Fig. 4.

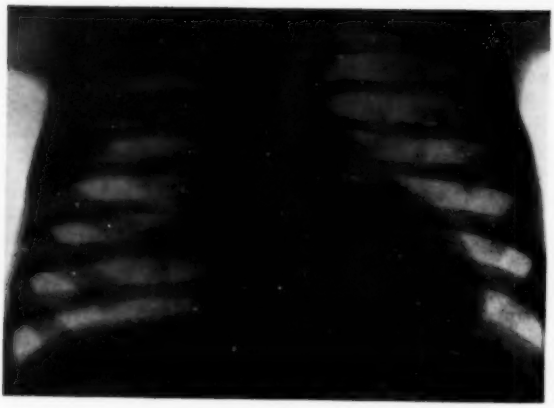

Fig. 5.

it was of hard consistency (Fig. 1). The abdomen was swollen. Inguinal and cervical lymph nodes were palpable. There was no pathologic sign pertaining to the respiratory, circulatory, nervous, and skeletal systems.

X-ray examination of the skull revealed two bone lesions, each having a diameter of a 50-cent piece. One was on the frontal, the other on the right parietal bone. Two other smaller lesions, one on the sixth rib and the other on the tuberositas tibia level of the right tibia bone, were present (Figs. 2, 3, 4, 5). The x-ray taken on Feb. 25, 1954, revealed that the defect on the parietal bone had reduced to one-half of its original size (Fig. 6). The x-ray examination on March 25, 1954, brought out enlargement of the old lesions, as well as the appearance of smaller new lesions on the parietal bone. Still greater enlargement of the old defects and the addition of new ones, both on the parietal and the frontal bones, were observed in the x-ray film of May 8, 1954 (Fig. 7). No change in size or number was observed in lesions of bones other than the skull.

Laboratory examinations revealed the following: The specific gravity of the urine never exceeded 1.005. In the several concentration tests performed, the highest density recorded was 1.012, and there was no decrease in the amount of urine passed. No pathologic changes were observed in the myelographic study made on Dec. 30, 1953. The fragility of the red cells started at 0.5 per cent and ended at 0.3 per cent. Bleeding time was normal. Blood chemistry: Sugar was 89 per cent (Nov. 30, 1953). The sugar tolerance test was within normal limits. Calcium was 7 mg.; anorganic phosphates, 4.5 to 5 mg.; alkaline phosphatase, 22 to 36 Bodansky units; sedimentation rate, 9 mm. in 30 minutes, 27 mm. in one hour.

Blood cultures remained sterile. The cerebrospinal fluid was normal.

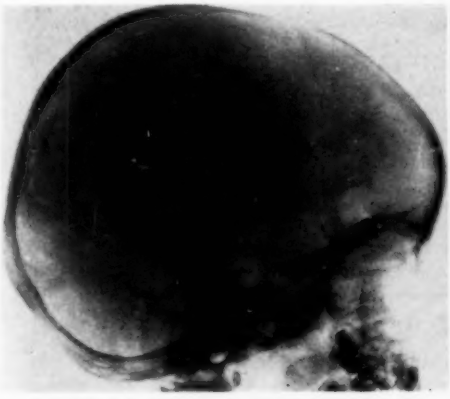

Fig. 6.

Fig. 7.

Bordet-Wassermann, leishmania, and plasmodia tests were negative. The Mantoux test (1/100) was positive.

Virus cultures of feces and urine proved negative. Blood pressure was 75/55 mm. Hg. Electrocardiogram was normal. Takata-Ara test 1/16 (+++); 1/216 (++). Cadmium was 1 plus. Lipoid bodies were absent in the microscopic examination of the urine sediment.

Course of the Disease.—After some time the purpuric spots faded and were replaced by mild pigmentation. However, attacks of petechiae, and

their subsequent fading, were repeated from time to time. Because of itching, the patient scratched the spots and provoked their bleeding.

Exophthalmia was first observed three weeks after admittance to the clinic and gradually became more prominent.

The lymph nodes were moderately enlarged. Their size slightly decreased for a while, but no essential change occurred. The biopsy result of a left inguinal lymph node was as follows: Microscopically, the follicular structure of the lymph node was completely altered. Cells resembling

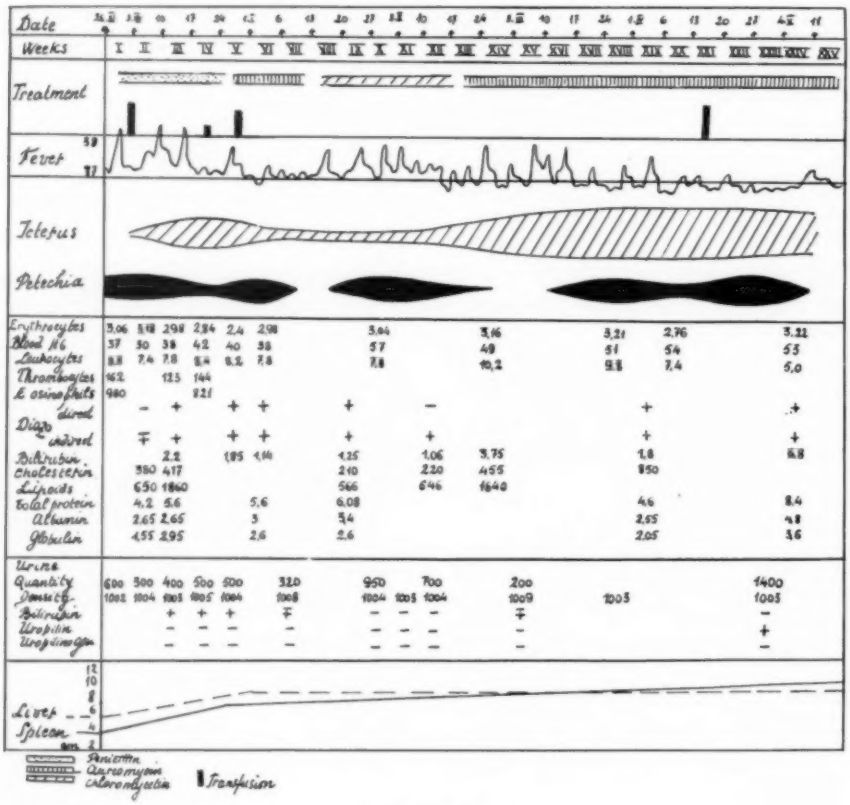

Chart I.

Splenomegaly increased in a short period of time and the spleen reached the level of the umbilicus. No further enlargement occurred.

The liver also increased in size, accompanying the splenomegaly. Nodules of the size of almonds were palpable on the liver. It was of hard consistency.

lymphocytes were present. Larger elements, resembling the plastic cells of the blood, poor in protoplasm, having round nuclei relatively rich in chromatin, were also present. Among these latter cells, and resembling them in character, were also giant cells with two or three nuclei. In all microscopic fields, a great number of

reticulum cells with large nuclei poor in chromatin were observed. The blood sinuses were large and the endothelial cells swollen. Probable diagnosis: Reticulosis (Dec. 16, 1953).

Jaundice also appeared and was superimposed on the earthly pallor of the patient. The jaundice increased and decreased in intensity periodically. One month after admittance to the clinic, collateral veins appeared on the abdomen.

The fever showed subfebrile rises, lasting a few days, at three- to four-week intervals.

Treatment.—From Dec. 3 to Dec. 25, 1953, penicillin therapy was administered. The dose used was 500,000 I.U. the first five days, followed by 200,000 I.U. daily. From Dec. 25, 1953, to Jan. 17, 1954, 200 mg. per day of Aureomycin was given orally; total dose, 4.6 grams. From Jan. 17 to Feb. 22, 1954, 400 mg. per day of Chloromycetin was given orally; total dose, 14.4 grams. From Feb. 22 to May 10, 1954, 400 mg. per day of Aureomycin was given orally. Transfusions, vitamins, and hepatic extracts were also administered to the patient.

DISCUSSION

Thus we see two main groups of symptoms in the case: symptoms that agree with the Abt-Letterer-Siwe disease; and those that agree with lipoid granulomatosis. Before analyzing each symptom separately, we summarize the case as follows:

Otorrhea, fever, and skin eruptions constituted the initial symptoms. Later, polydipsia and polyuria appeared.

Clinical and laboratory examinations revealed hepatosplenomegaly; progressive hypochromic anemia that did not respond to any form of treatment; diabetes insipidus, which became more and more prominent; and typical lesions in the bones. The biopsy report revealed a histologic structure typical of reticuloendotheliosis.

Schafer[8] collected thirty-six cases up to 1949, including his own cases, and reported twelve of them to be intermediary types.

In the beginning of the disease, an otorrhea existed. In the reports of many authors, such as Ter Porten, Van Creveld, and Letterer, the existence of otorrhea is cited.

Considering this fact, many authors described this disease as an infectious reticuloendotheliosis. Infections like histoplasmosis capsulatum, mycosis fungoides, and sporothricosis cause the formation of local granuloma, as well as a general hyperplasia in the reticuloendothelial system.[10] Some others do not consider these infections as the origin of the disease. They regard the disease as a failure or lack of resistance that arises from the insufficiency of the reticuloendothelial system, and even as a necrosis and total loss of the granulation tissue. Glatt, Lichty, and Grady-Stewart state that because of the granulomas the disease reminds one of chronic otitis.

Some authors discovered this disease in tuberculous children. In our case, the tuberculin test was positive. The x-ray of the lungs showed massive hilar shadow. However, it is not easy to estimate whether these radiologic findings are due to tuberculosis or to the existing disease. Some cases of the Hand-Schüller-Christian disease with fibrous changes in the lungs and even presenting a pseudogranular aspect have been reported. The various blood cultures made from our patient remained sterile. Bacteriologic examination of material from the otorrhea revealed Klebs-Loeffler bacilli. The only in-

fection obvious enough to be cited is tuberculosis, as shown by the positive tuberculin test.

The cutaneous elements in the Abt-Letterer-Siwe disease are of petechial and papillar quality. Their preference of localization is the trunk. In rare instances they are found on the scalp and extremities. Cutaneous signs are not accompanied by any other signs of hemorrhagic diathesis. We also, in our case, have recorded normal bleeding and clotting times, and a normal thrombocyte count. Lacet (Rumpel-Leede) was positive in our patient. Once when the head was lowered for a venous puncture from the neck, an onset of petechiae occurred. The purpuric reaction of the patient can be partly explained by his nutritive state and partly by the vascular changes brought about by the reticuloendotheliosis.

Tartar was present on the teeth, a usual symptom in exudative diathesis. There were caries only in the upper incisors. However, Bessiere and associates[13] have declared that the disease can start with signs of gingivitis resembling scurvy.

Fever started simultaneously with other signs. Authors who reject infection as an etiological factor are of the opinion that the cutaneous signs precede the fever.[8] In the history of our patient, we have been unable to clarify this point. The patient manifested atypical fever during part of his stay at our clinic.

Hepatosplenomegaly was obviously present. When the patient was first admitted to the clinic, the spleen exceeded the costal margin by 2 fingerbreadths and was later 11 cm. on the medioclavicular line.

Moderate adenopathy was present. It decreased for a period of time, and has again recently increased.

Bone lesions can be identical in character in all three types of reticuloendotheliosis. It is usually impossible to identify each, radiologically.

One of the elements of the classical triad in the Hand-Schüller-Christian disease is diabetes insipidus. In our case, no change was observed on the sella turcica contours in the beginning but the most recent x-ray study revealed bone lesions in the sella turcica area. In fact, corresponding increase in polydipsia and polyuria was noted recently. However, diabetes insipidus is not only the result of an involvement of the sella turcica, but also of various changes outside of it. Among these various changes are xanthomatous foci on the dura around the hypophysis, xanthomatous inflammatory processes on the neurohypophysis, and changes of the same type on the infundibulum and the tuber cinereum.[14] In our patient, diabetes insipidus symptoms started before any bone destruction in the sella turcica area was apparent in the x-ray films. Therefore, it seems logical to accept the fact that the factors causing diabetes insipidus affected the hypophysis first and the skeletal system later.

Lymphadenopathy remained moderate. The biopsy of an inguinal lymph node showed an increase in reticular tissue and alteration in the lymph node structure. In our patient, "foam cells," usually seen in the Hand-Schüller-Christian disease, were absent. However, according to Freud,[15] these cells are not seen at

the beginning of the disease, and according to Gross-Jacox, Feud, Grossmann, Dragutsky, and others, these cells are not a regular histologic finding. In a lymph node biopsy made fourteen months prior to death, Freund and Ripps failed to diagnose a case of the Hand-Schüller-Christian disease until the time of the autopsy, when they found typical foam cells at the lungs and the paravertebral fascia. Even at this stage, nothing different from the first biopsy results was obtained from the lymph node studies. P. Freud states that changes in the lymph nodes pertaining to nonlipoidic reticuloendotheliosis are not observed until one year after the start of the disease. Michaud and associates[16] differentiate this particular group where the histologic changes are gradual from the other xanthomatoses where the changes are more sudden.

In most cases of the Hand-Schüller-Christian disease, the blood cholesterin level is around normal values. Emphasizing this point, Thannhauser and Magendantz[22] have named reticuloendothelioses which show a normal blood cholesterin level in addition to the cardinal symptoms of the triad, "essential xanthomatosis of the normocholesterolemic type," and have grouped the high blood cholesterin cases under the name of "lipoid granulomatosis." Rowland[23] considers the high blood cholesterin level as the result of a primary defect of the cholesterin metabolism. Some authors are of the opinion that the increase in blood cholesterin results from necrosis of the granulomatous lesions.[17] According to these authors, the rises in fever in the course of the disease are related to this necrotic process, and they state that there is an increase in the blood cholesterin level during the febrile periods. In our patient, the blood cholesterin level remained high after the fever subsided. There was even a slight increase. Therefore, no parallelism existed between the rise in temperature and the increase in blood cholesterin.

There was obvious hypochromic anemia in our patient. The leukocyte count was around normal values. Ten days after admittance to the clinic, mild jaundice developed. At the beginning, indirect Diazo test in blood was positive. The jaundice gradually increased, and finally the urine became bilirubin-positive. There existed a parallelism between the development of the jaundice and the increase in anemia. Most probably this relation was due to increased erythrocyte destruction. Veslot and co-workers[18] have observed jaundice in their patients and have declared this to be a peculiarity of the case.

From the prognostic point of view, the disease is lethal. Cases of survival are rare. Regarding the few patients who have survived, each author considers his own method of therapy as effective. Willi and Müller[24] cite x-ray as the effective factor in therapy. These authors have applied indirect x-ray to their patient, after the Cignolini method. Observing improvement in the general state and disappearance in cutaneous lesions, they have continued the treatment with direct x-ray, despite the progression of the bone lesions. These same authors advise the continual of the x-ray therapy until spontaneous cure occurs. Wallace[19] also has treated all seven of his patients using the same method.

The appearance of jaundice in our patient made us suspect the presence of infectious hepatitis, in view of cases of infectious hepatitis in the clinic. Consequently, we started using Aureomycin instead of the inefficacious penicillin. From Dec. 19, 1953, until Jan. 15, 1954, we administered 30 mg. per kilogram of oral Aureomycin and subsequently 50 mg. per kilogram of Chloromycetin.

The general state of the child was too poor to apply teleradiotherapy. Therefore, we considered using P^{32}. However, the patient improved after the Aureomycin and Chloromycetin treatment. Some of the authors who are of the opinion that infection is the etiological factor in the Abt-Letterer-Siwe disease as Aronson,[25] and Bierman and associates[20] have given antibiotics to their patients, and report favorable results especially with Aureomycin, Chloromycetin, and streptomycin.

We do not share the opinion of these authors who report the favorable results of the antibiotics. Our patient, who has been under continuous antibiotic therapy, is growing worse every day with progressing symptoms of the disease.

The fact that cases which stand between the Abt-Letterer-Siwe disease and lipoid granulomatosis are relatively rare, and the fact that we have been unable to obtain, by antibiotic therapy, the favorable results reported by others, has led us to publish this report.

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LYMPHOEPITHELIOMA

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LYMPHOEPITHELIOMA of the nasopharynx is an uncommon malignancy in childhood. Because it should be considered in the differential diagnosis of causes of cervical lymphadenopathy, the report of the following case is thought to be warranted.

CASE REPORT

A 10-year-old white female was referred to this hospital for evaluation of her cardiac status. During childhood she had frequent upper respiratory infections. At the age of 5 she had pertussis complicated by pneumonia, with cyanosis noted on coughing. Cardiac enlargement and a murmur were discovered during this period and thereafter she was followed in a cardiac clinic.

In March, 1952, a small mass was first noted in the left side of the neck. This was not painful but grew progressively larger. In July, 1952, hospitalization was advised and she was admitted to another hospital. Hypertrophied tonsils and a large, freely movable, hard, lobulated painless mass in the left side of the neck, not adherent to the skin, and several enlarged lymph nodes on the right were recorded. A cardiac murmur was described. A tuberculin patch test and chest x-rays were within normal limits. The electrocardiogram was reported to be normal. Antibiotics were given for the tonsillitis. The child was discharged as unimproved and the final diagnoses were carcinoma of the neck and congenital heart disease.

In September, 1952, there was continued growth of the neck mass, producing pain along the mandible radiating upward into the preauricular area, and itching of the left ear. Difficulty in swallowing was present and weight loss was marked. The child was again hospitalized for reevaluation. She was subsequently discharged as improved with the final diagnoses of tuberculous adenitis, and congenital heart disease.

In the interval prior to her admission to Hahnemann Hospital on Nov. 3, 1952, her voice had become progressively more hoarse and nasal. Mouth breathing was constant and the child had difficulty in swallowing. She lost about ten pounds during the eight-month period following the appearance of the neck mass.

On physical examination on admission she was found to be thin and pale and appeared ill. Respirations were labored. The left external auditory canal contained a cheesy, cream-colored exudate and the drum was perforated. A preauricular node 1 cm. in diameter was present with swelling and tenderness of the surrounding area.

The mucous membrane of the nose was hyperemic and the turbinates swollen. A purulent discharge was present. A glistering silvery gray mass was present on the left, filling the choana and extending one-fourth of the way anteriorly. On the right a smaller mass partially blocked the passage. The tonsils were hypertrophied, the left more so than the right and it appeared to be firmer and whiter. A firm, nodular nontender mass was present on the left side of the neck, extending from the supraclavicular area to the postauricular area along the course of the sternocleidomastoid, which was not separately discernible. It was firmly

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attached at the upper pole but at the lower pole slight lateral motion was possible. The anterior chain of nodes on the right side of the neck was moderately prominent to palpation.

There was a systolic thrill palpable in the fourth and fifth left interspaces. Best heard over the lower sternum was a moderately loud, harsh systolic murmur which was transmitted over the left anterior chest.

Laboratory examination revealed the following: The erythrocytes showed a progressive fall during the hospital stay from 4.4 to 3.2 million per cubic millimeter. Hemoglobin dropped from 12.8 to 10.3 grams. Leukocytes fell from 19,000 to 8,000 with polymorphonuclear cells predominating. Moderate amounts of protein were constantly present in the urine and on one occasion there were large numbers of red cells. Culture of material from the ear showed diphtheroid bacilli and some staphylococci.

Fluoroscopy and films with barium swallow revealed a soft tissue swelling in the base of the left side of the neck with no deviation of the esophagus or trachea. No pulmonary parenchymal abnormalities were present. The peripheral pulmonary vascular markings were normal. The main pulmonary artery was somewhat dilated and the right branch was prominent. The heart was not enlarged but the apex was elevated and rounded. X-rays of the nasal accessory sinuses, mastoid, and facial bones revealed a nasopharyngeal mass visualized on the lateral films. There was no evidence of metastatic bone change. There were no lesions of the long bones. An intravenous urogram was normal.

The electrocardiogram showed right ventricular hypertrophy and strain.

A biopsy of the preauricular node was quickly obtained. The pathological diagnosis was "metastatic lymphoepithelioma." A nasal lesion biopsy specimen was of similar structure: a thin collagenous stroma in which were seen many small lymphocytes with large island of reticulum cells. The diagnosis of lymphoepithelioma was established. Immediately after the biopsy, irradiation was begun, and within two days there was marked subjective and objective improvement.

On Nov. 23, 1952, gross hematuria occurred. Examination revealed no obvious external bleeding point or vaginal bleeding. The blood urea nitrogen, an intravenous urogram, cystoscopy, and complete peripheral blood studies were found to be within normal limits.

X-ray therapy in the meantime had been continued. Lateral skull films at this time revealed marked resolution of the nasopharyngeal mass. On Dec. 30, 1952, the child was discharged, having received 3,060 r at a midline point of the oropharynx and 2,536 r to the cervical nodes. Examination on discharge revealed some tumor tissue as a thin gray line delineated from the normal septum in the right nostril. The mass in the left cervical area now consisted of numerous firm, irregular nodules. There was moderate cervical adenopathy on the right.

Following her discharge, the child had relief of pain and deafness for a number of weeks. On Jan. 8, 1953, she was seen in the tumor clinic. Her appetite was good, she had gained one pound, and her energy was gradually increasing. There was no appreciable change in the size of the left cervical mass and one small node in the right neck was still palpable.

When the child was again admitted on Feb. 10, 1953, she had lost two pounds in weight. There was ptosis of the left upper lid and the eye protruded. A mass was noted in the left nasopharynx. Third nerve palsy was noted on the left and the pupil was dilated and fixed. Fourth and sixth nerve weakness was present on the left. There was marked posterior cervical adenopathy. The nodes were not tender.

X-rays revealed an increase in the retropharyngeal soft tissue mass as compared with the films taken prior to her discharge. The floor of the middle fossa in the region of the petrous apex was eroded over an area slightly more than 3 cm. in diameter.

X-ray therapy through the orbit was begun, and after a few days there was marked improvement. The pain and ptosis disappeared and proptosis diminished. The child was happier and symptomatically greatly improved after ten days of therapy, totaling 950 r (air) directly through the left orbit and 250 r (air) to the petrous portion of the left temporal bone. She was discharged to return in one month. The palliation for which we hoped had been achieved and it was considered that she had made an excellent response to therapy but that the prognosis for survival was poor.

Another month later it was reported that the child was gradually deteriorating, and she was again hospitalized in her home town. Bilateral proptosis, blindness, difficulty in breathing and swallowing, and bilateral anterior and posterior cervical adenopathy were noted. For six weeks she lingered in severe pain, in spite of morphine, but with hearing and intellect acute. Terminally she had numerous convulsions. Death occurred six months after she was first seen by us and fourteen months after clinical evidence of metastasis was present. Post-mortem examination was not performed.

DISCUSSION

Lymphoepithelioma of the nasopharynx is notoriously difficult to diagnose in the earliest stages. The primary tumor appears first in the form of a small, freely movable nodule with the same consistency as the surrounding tissue. The overlying mucosa is of normal color. After a period of slow growth, there is rapid acceleration. The tumor may then ulcerate and bleed. Cervical metastasis is present early, usually before the primary tumor is discovered.[3]

This type of tumor occurs predominantly between 20 and 40 years of age, usually in the male.[5] The primary tumor remains small for a long period and at times is clinically silent. Apical abscess, otitis, and trigeminal neuralgia are frequently diagnosed, followed by extractions, myringotomies, and other surgical procedures without relief. Since cervical adenopathy is the most common first sign, biopsy is frequent, but it is obvious that although cancer is found on biopsy of a cervical node, a complete diagnosis cannot be made until the primary lesion, which is so frequently missed, is found.

We know that cancer of the head and neck is less than 1:100 times as frequent in children as in adults. Dargeon[6] reported seven tumors of the nasopharynx in his series of 218 cases of cancer in children observed at the Memorial Hospital in New York, or 16 per cent of the tumors of the head and neck, second only to retinal glioma in frequency in this region. Histologically these were lymphoepitheliomas or transitional cell carcinomas. This type of tumor has a peculiar structure and is extremely radiosensitive, resembling in structure the so-called lymphoepithelial organs of Jolly,[3] the thymus, the tonsils, etc. They consist of sheets of cells with pale-staining nuclei and hyperchromatic nucleoli, often in syncytia and always infiltrated with lymphocytes.

Trotter[10] pointed out that these tumors cause cranial nerve symptoms.

The proximity of the lesion to the eustachian tube causes deafness, one of the earliest symptoms. The involvement of the third division of the fifth cranial nerve causes pain radiating to the ear, the lower jaw, the tongue, and the face. Other divisions are later involved. Further extension produces paralysis of the other nerves: that of the fourth and sixth causes squints; the third producing ptosis and paralysis of the masseter, temporal, and pterygoid muscles, thus causing difficulty in mastication. Involvement of the jugular foramen will bring about paralysis of the ninth and tenth cranial nerves with resultant dysphagia, vocal cord paralysis, and alteration of voice. Direct metastasis to muscles, bones, nerves, and distant viscera also may take place.

Since a sarcomatous tumor is most frequently thought of in a child, it is important to differentiate a lymphosarcoma of the nasopharynx from a lymphoepithelioma of the same site. With sarcoma there is an earlier age incidence, most cases occurring between 15 and 30 years of age; the sex incidence is equal; the primary growth is never silent, it forms a bulkier tumor and gives rise to nasal obstruction, bleeding, and bulging of the soft palate. The course of the disease is shorter, death occurring in a few months. Metastases occur to the lymph nodes and to the lungs.[5]

The prognosis is almost always grave in nasopharyngeal lymphoepitheliomas, although palliation with radiation is very effective. In Dargeon's[6] series, five of the seven patients were free of disease after two weeks to three months of treatment, but six of the seven patients eventually developed generalized metastases and all seven died. The average duration of life after the first symptom was twenty months. Coutard[2] reported that (in adults) the proportion of females with lymphoepithelioma of the tonsillar region, hypopharynx, and larynx, was small compared with the proportion of males affected by these lesions. Of 212 treated, 197 were males and 15 females. The cure of these epitheliomas was more readily accomplished in women than in men, since up to January, 1931, out of 15 women treated, 9 or 60 per cent were free of disease from four to nine years, whereas the proportion of men treated during the same period (1920 to 1926) and free of symptoms at the same time (1931) was only 33 out of 197 or 16 per cent.

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LAURENCE-MOON-BIEDL SYNDROME

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A REVIEW of the American pediatric literature of the past ten years reveals the fact that only one article has been written describing the Laurence-Moon-Biedl syndrome in the United States. In that paper, Likens and associates[1] reported two cases of Laurence-Moon-Biedl syndrome in siblings, and reviewed the literature on the subject.

This case represents a classical example of Laurence-Moon-Biedl syndrome that recently was seen by one of us.

CASE REPORT

M. K., a 6-year-old white male, was admitted to the pediatric service with the chief complaint of obesity (Fig. 1), and diminishing vision. Past history revealed that the patient was born with bilateral postaxial polydactylism (Fig. 2). No other abnormal findings were noted at birth except for obesity. At 3 years of age, a physician was consulted because of marked obesity and hypogenitalism, and treatment consisting of weekly injections of 500 units of A.P.L. (anterior-pituitary-like hormone) was instituted. This form of therapy was continued for three years without any reduction in weight or increase in size of the genitals.

Eighteen months prior to hospitalization, it was noted that the boy had difficulty in seeing and in locating objects. An ophthalmologist prescribed glasses at that time, and his vision became somewhat improved.

Family history of obesity, polydactylism, visual disturbances, and mental retardation was denied either in the siblings or in the immediate family.

Physical examination revealed the following pertinent findings: marked central obesity, rounded facies, hypogenitalism, descended somewhat small testes, lack of pubic and axillary hair, polydactylism of right hand, scar evident where surgery had been performed on left fifth finger, and a blood pressure of 100/70. There was a peculiar high-pitched childish voice.

Laboratory data showed a normal urinalysis, hemoglobin 12.1 grams, red blood count 4,720,000, white blood count 10,550, polymorphonuclear cells 49, lymphocytes 40, monocytes 7, eosinophils 4. X-rays of chest, long bones, and skull were all within normal limits. Electroencephalogram reported no abnormalities. Circulating eosinophil count (ACTH test) was: control 144 per cubic millimeter and experimental 22 per cubic millimeter. Urinary 17-ketosteroids was 2.35 mg. per twenty-four hours.

The patient was put on a 1,000 calorie diet. Psychologic evaluation was carried out, which revealed a highly deviant mental development, in many areas at a defective level. Mental age was 4 years 5 months, with an I.Q. of 66. Ophthalmologic consultation was obtained, and funduscopic findings were "arterial attenuation and scattered definitive areas of pigment proliferation, consistent with diagnosis of Laurence-Moon-Biedl syndrome." The patient was discharged on desiccated thyroid ¼ grain O.D. and 1,000 calorie diet. Parents were informed of the poor prognosis.

Final diagnosis: Laurence-Moon-Biedl syndrome.

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Fig. 1.—Characteristic configuration with the central obesity, genu varum, and hypogenitalism.

Fig. 2.—Note the polydactylism of the right hand.

DISCUSSION

This is a case presentation of a rather unusual and an uncommon syndrome, namely, the Laurence-Moon-Biedl syndrome. Because of its rarity, we feel that this report is warranted in order to help the pediatrician become more conscious of the disturbance.

The etiology of the Laurence-Moon-Biedl syndrome is obscure, but it is generally believed to be due to a hypofunction of the hypothalamus, probably resulting from familial and genetic factors. The hypogonadism is thought to be secondary to failure of the central nervous system to activate the pituitary gonadotropic mechanism.[2] Just as the gonads will fail to develop unless stimulated by pituitary gonadotropic hormones, the pituitary will fail to develop gonadotropic activity unless activated by neurological stimuli.

It is interesting to speculate as to the cause of the failure of the genitals to enlarge following a three-year course of A.P.L. Is this due to a lack of end organ response on the part of the genitals, or is it due to the fact that the defective hypothalamus is unable to activate the pituitary gonadotropic axis which results in genital enlargement? The latter would seem to be the more likely course, in view of the fact that even infants can be stimulated to produce pubertal changes with estrogens and androgens.

SUMMARY

A classical case of Laurence-Moon-Biedl syndrome in a 6-year-old child is presented. It satisfies the five cardinal diagnostic criteria of Warkany,[3] namely: (1) obesity, (2) mental retardation, (3) polydactylism, (4) retinitis pigmentosa, (5) genital hypoplasia.

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Medical Progress

HOMOLOGOUS SERUM JAUNDICE

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LAST spring, in connection with some rather extensive surgery, I was given seven pints of blood in four transfusions. Two and one-half months later, while still thirty pounds less than my usual weight, I developed marked jaundice and had to return from the country to the hospital. My internist, who was about to go on his vacation, turned my case over to a liver expert, who at the first visit said to me: "You're seriously sick, and you are going to be very miserable and very depressed." That may be a wise way of greeting some patients, but at the time I wondered if it applied to me. I was feeling only tired and dopey, and certainly no busy person is exactly overjoyed at the prospect of spending the better part of the summer on his back in a hospital bed. I had plenty of time in the next few weeks not only to read up on homologous serum jaundice but also to think about doctor-patient relationships and, in general, about being a patient. I would like to share my thinking with you.

Viral hepatitis infections, with our present meager knowledge, may be divided into two types: infectious hepatitis, formerly called catarrhal jaundice, a contagious disease due to a specific virus known as the hepatitis virus A and probably contracted usually via the oral alimentary route, and serum hepatitis, also called homologous serum jaundice or postinoculation jaundice, usually a noncontagious infection and due as a rule to transcutaneous inoculation by injection of a human blood product containing the hepatitis virus B. It is to be hoped that these broad classifications may be more clearly defined when serologic and other tests become available.

The two conditions, infectious hepatitis and serum hepatitis, are indistinguishable as to pathology and symptomatology but have certain immunologic differences and differences as to incubation period, the presence of the virus, etc., which will be mentioned in due order. This talk, however, will deal mainly with homologous serum jaundice because the speaker can deal with it both objectively and subjectively.

Virus B is present in whole blood, in serum and plasma, and in fibrinogen, thrombin, and prothrombin. It is not contained in serum albumin or in globulin prepared by the present ethanol fractionation method and with the heating of the albumin to 60° C. for ten hours. In whole blood or serum it is variably estimated as present in 0.3 to 0.8 per cent of specimens, or in one out of two or three hundred transfusions, and as little as 0.01 c.c. is sufficient to cause infection if given parenterally. One to 2 per cent of pools of five to ten plasmas are infectious, and for the large pools of

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several hundred plasmas that are usual in the United States, the incidence can be as high as 10 or 12 per cent.

There is no mechanism for detecting the presence of virus B in a donor's blood except by human volunteer experimentation, nor is there any practical method of destroying the virus in a blood donation. A thymol turbidity test of over 4.0 has been of some slight aid apparently in ruling out donors who may have the disease, although if used in this way it excludes many donors who are not carriers. Preservation of blood products by freezing or by lyophilizing preserves the virus also. Virus B is apparently less affected by ultraviolet radiation than is virus A, and this process cannot be relied on for sterilization. On the other hand, if a lot of plasma is kept at room temperature for six months or more viruses tend to die out, and even if a lot is deliberately contaminated with a plasma known to contain virus B, the virus apparently is slowly inactivated in a period of over six months.

Not everyone given infected blood develops homologous serum jaundice. A variable proportion of adults, perhaps reaching 50 per cent in some areas, has developed immunity from previous inapparent infections. Of the susceptible persons, perhaps one-half the adults and an even higher proportion of infants and children who are given infected blood or plasma may develop serum hepatitis without jaundice, and only the remainder will develop jaundice. Women over 40 years, pregnant women, and persons with impaired nutrition or with preexisting liver damage appear to be those most likely to develop jaundice and the more severe infections. The virulence of the virus also appears to be a factor, a virus that has been attenuated by ultraviolet light or other means apparently causing a longer incubation period than usual and less severe manifestations.

In patients with serum hepatitis the virus is present in the blood throughout the period of clinical manifestations and probably for a long time afterward, as long as five years in one instance. In another person it was found in the blood ninety days before the onset of clinical manifestations. This extensive viremia in serum hepatitis is somewhat in contrast to infectious hepatitis in which the virus is present in the blood only a week or two at the time of maximum symptoms. However, in this latter form of hepatitis the virus is present in the stool, which is not the case in serum hepatitis. In the incubation period also, the two forms of hepatitis differ appreciably. In infectious hepatitis the period averages fourteen to thirty-five days, whereas in serum hepatitis the usual period is somewhere between one and one-half and five months, the more serious cases often having had the shorter periods. A mild case due to an attenuated virus followed an incubation period of 196 days.

The pathological lesions of the two forms of hepatitis are the same. There is extensive destruction of the liver parenchymal cells, particularly the central cells in the lobules, together with much reticuloendothelial involvement. The liver becomes congested and swollen, especially in the period of early jaundice, and there may be some portal obstruction. Bile may or may not be taken up by the circulation to cause clinical jaundice. The spleen is occasionally enlarged, and in some

cases the lymph nodes generally become palpable. The destructive process of the liver cells is usually reversible to complete recovery, but may go on to a chronic hepatitis or to death.

The blood count is that of most virus diseases, the white blood cells rarely being over 12,000 in number with a relative increase in lymphocytes. In the fatal cases a marked leukocytosis may develop.

The clinical manifestations are indistinguishable in the two types of hepatitis. Three stages are usually described. The prodromal or preicteric stage varies from three or four days to a week or more and is characterized by two groups of manifestations, those due to a virus infection and those due to a liver disturbance. The former consists of fever which may last five or six days, headache, and general malaise. The liver is likely to become swollen and tender, and there may be constipation or diarrhea, nausea or vomiting, a bad taste in the mouth, and, most common of all, marked loss of appetite. The urine becomes dark in color as the bilirubinuria develops and the stools become lighter in color, but it is unusual to have completely clay-colored stools in hepatitis. Presently icterus appears in the sclerae as the icteric stage develops. Jaundice in the skin follows and reaches its height usually in three or four days, although it may not do so for two weeks or more, and then it fades slowly, the total duration lasting from a week to three to six months. There is no correlation between the severity of the hepatitis and that of the jaundice, which may not be readily seen in some patients who are otherwise quite sick. Depression is in many patients marked and lasts for weeks, sometimes long after the acute manifestations have cleared up. The period of convalescence is likely to be protracted, and the return of strength and energy is tediously slow. Appetite remains poor for some time but then changes to a state of voraciousness.

In children, hepatitis of either type is likely to be relatively much milder than in adults, and as a result a much smaller percentage of children with

TABLE I. VIRAL HEPATITIS

Name of entity	Infectious Hepatitis (IH)	Serum Hepatitis (SH)
Synonyms	Catarrhal jaundice	Homologous serum jaundice
Cause	Hepatitis virus A	Hepatitis virus B
Infection by oral route	+	0
Infection by parenteral route	+	+
Onset (variable)	Abrupt, febrile	Insidious, afebrile
Viremia	A few days	Many months, or years
Virus in stools	+	0
Cross-immunity	0	0
Protection by gamma globulin	+	Prob. 0
Incubation period, days	14 to 35 ±	55 to 100 ±
Normal age range	Below 30	All ages
Pathology		
Clinical manifestations	Not clearly separable	
Prognosis		

cases is hospitalized. Instances of viral hepatitis without jaundice are more common. The onset of the disease is accompanied by more vomiting but with less anorexia and less often with fever. The jaundice, if present, is usually shorter in duration, and there is less danger in allowing activity out of bed after the first two weeks.

In adults the mortality of virus hepatitis of either type may be 5 to 15 per cent; in children it is usually much less.

The hepatitis viruses can cross the placenta so that a baby born icteric need not necessarily have a congenital anomaly of its bile tract.

The diagnosis of serum hepatitis is usually facilitated by the history of an injection of human blood, serum, or plasma or of an inoculation with some human serum product such as a yellow fever vaccine, which has been buffered with infected serum, or by a history of working with infected syringes in a laboratory. Ninety-five cases have been reported of laboratory workers who have been infected with virus B while at work, and in World War II nearly a whole regiment was infected by yellow fever vaccine that had been buffered with human serum which, unfortunately, had been donated by a man who had had jaundice. Other causes of jaundice should, of course, be ruled out, such as those that are due to biliary obstruction by gallstones or cancer. Slight jaundice may develop in infectious mononucleosis in which hepatitis may coexist, and, on the other hand, acute hepatitis without jaundice may have a slight rash in the prodromal stage which is suggestive of mononucleosis.

The prognosis of serum hepatitis is generally excellent if complete rest is taken until the tests for liver function have returned to normal. Relapses occur in from 2 to 18 per cent of the cases, and a chronic state of hepatitis may develop, especially when there is activity too soon, or too early indulgence in alcohol, or if ether anesthesia is used. The liver damaged by virus infection is more vulnerable than normally to other hepatotoxic agents. The mortality rate of serum hepatitis averages around 5 to 15 per cent in different series, most deaths occurring in the second week of clinical manifestations, but some may not take place until after a month or two of illness.

After one infection with virus B, there probably is immunity against future infections, but no cross-protection between virus A and virus B has been definitely determined. Virus A infections can be prevented by small injections of gamma globulin, as little as 0.01 c.c. per pound of body weight being usually protective if given more than seven days before the expected time of onset of symptoms. There is no proof that gamma globulin is effective in preventing virus B infections.

To hold down the incidence of serum hepatitis, transfusions should be given only when really necessary, and pooled plasma should be kept under sterile conditions at room temperature for at least six months before being used. All syringes that have contained any human blood serum or plasma should be carefully washed with soapy water, then sterilized by boiling for at least ten minutes, or autoclaving under steam pressure, or baking in a hot oven. Needles can be sterilized by flaming, but attempted sterilization by any antiseptic solution is not adequate. When blood is being drawn from a number of persons in succession, each

syringe, in addition to the needle, must have been sterilized. When blood is taken from a vein with a syringe, some of the blood is inevitably sucked back into the vein when the tourniquet is released. If the syringe is not sterile, the patient is exposed to infection.

Laboratory workers, nurses, and others handling infected syringes and needles should be especially careful to avoid even the slightest pricks or scratches of the hands because undoubted infections with serum hepatitis have been contracted by that method.

The choice of laboratory tests naturally depends on what information is desired. Bilirubin is the principal pigment in bile. When in the blood, it is the responsible agent for the appearance of jaundice; when in the urine in excess, it causes a dark color. Urobilin, the cause of the normal color of urine, is a pigment derived from urobilinogen, which in turn is derived from bilirubin. Therefore, one can determine the amount of bilirubin in the blood which is normal up to 0.8 mg. per 100 c.c., or one can take an icteric index, which is normal up to five. For excess bile products in the urine we examine for bilirubin with the simple foam test or for urobilinogen, the normal being less than 2 mg. in twenty-four hours. If we suspect a hepatitis even though there is no apparent jaundice, all these tests are helpful. In a jaundice due to blood hemolysis as in hemolytic anemia, there is no obstruction and the van den Bergh test is negative, that is, there is a direct or immediate reaction. If the biliary system is obstructed, we get an obstructive jaundice and a positive van den Bergh test, that is, an increase in the indirect test for bilirubin. In viral hepatitis, bile already formed may find obstruction in the bile canaliculi from the inflammatory condition in the liver and may find its way into the circulating blood, so the van den Bergh test may be positive early, showing obstruction, but it is later negative when the liver is healing. It is not a valuable test in viral hepatitis except for early differential diagnosis from a hemolytic anemia.

Tests for liver dysfunction that are of value and widely used are the cephalin-cholesterol flocculation test, the thymol turbidity test, and the bromsulphalein dye test. The cephalin test, when liver function is considered normal, is sometimes reported as zero, or plus or minus, and when there is decreased function, as one plus to three plus; or, like the thymol turbidity test, it may be reported as normal up to 4 units and abnormal over that amount. The thymol turbidity test is perhaps the most constant indicator of persistent liver disturbance. For each of these two tests and for the icteric index and van den Bergh tests, 4 to 5 c.c. of coagulated blood drawn before breakfast is all the laboratory needs.

The dye test is a little more trouble but gives a fair mathematical evaluation of liver dysfunction. Bromsulphalein (sulfobromophthalein sodium) comes in 3 c.c. ampules of a clear, nearly colorless solution which contains 50 mg. of the drug per cubic centimeter. In this test, 0.1 c.c. (or 5 mg.) per kilogram of body weight is injected into an arm vein about 8 A.M., the patient having fasted after midnight. Forty-five minutes later, 5 c.c. of blood is withdrawn from a vein in the opposite arm and is allowed to coagulate while being sent to a laboratory.

Special care during the injection should be taken not to spill any of the dye solution in the tissues around the vein because considerable pain would ensue for some minutes, radiating down to the fingers. Even in the vein, the dye may cause some smarting for a short period.

This is a test for function of the liver parenchymal cells, and a retention of 10 to 15 per cent or over is indicative of liver damage. Following an attack of serum hepatitis, the retention should be stabilized around 5 per cent or below before the patient is allowed to begin being erect or active.

TABLE II. SAMPLE RECORD

		NORMAL	7/15/53	7/22	8/4	8/11	8/17	1/20/54
Blood								
Bilirubin mg. %	Total	0.7-1.5	12.8	9.1	2.6	2.7	1.6	0.8
	Direct	0.2	8.8	5.4	1.3	1.0	0.7	0.1
	Indirect	0.5-1.3	4.0	3.7	1.3	1.7	0.9	0.7
Thymol turbidity units		<4	19	15				
Cephalin flocculation		<4	11				3	3
Bromsulphalein	%	10	80.5		20.3	13.8	10.9	3.0
Total protein	Gm. %	6.2-7.5	6.8	8.0	7.7			6.6
Albumin	Gm. %	4.0-5.5	3.6	4.2	4.5			4.2
Globulin	Gm. %	1.8-2.8	3.2	3.8	3.2			2.4
Urine								
Urobilinogen mg. in 24 hours 0.5-2 mg.			3.8					

During a viral hepatitis it is wise also to watch the concentration of proteins in the blood, especially in the albumin, which may become sufficiently decreased to warrant the giving of serum albumin. The normal total proteins is 6.2 to 7.5 Gm. per 100 c.c. and of serum albumin is 4.0 to 5.5 Gm. Low concentrations of serum albumin, including a reversed albumin-globulin ratio, point to defective synthesis in the liver and to a tendency to edema, as well as to ascites if there is appreciable portal obstruction. One or two units of serum albumin can be given each day for from two to three days until a more normal figure has been reached. This material can be given intravenously without fear of reaction and without pain to the recipient. It does not carry the serum hepatitis virus.

The treatment of viral hepatitis need not be complicated, but for the patient's best good neither should it be casual. Bed rest from the earliest possible day until the liver function tests have become stabilized at normal and until the liver is normal in size and no longer tender is essential to reduce the likelihood of relapses or of the development of a chronic hepatitis. In my case, this meant four weeks with at least one shoulder on a flat mattress, and I imagine I was lucky not to have this a longer period. There is some evidence that just a change to the erect position increases the demands on a liver. Sleeping should be encouraged by minimizing excitement and fatigue and perhaps by mild sedation. Visitors need to be rationed. The diet should be "high protein and high calorie," enough fat being allowed to make the diet as pala-

table as possible. Milk fat is usually well tolerated. Additional liver damage is minimized by banning alcohol, also ether anesthesia. Fluids up to 2 liters a day should be taken, and, if there is much vomiting, an intravenous injection of 5 or 10 per cent glucose may be desirable. The progress of the liver function should be watched by laboratory tests performed at least weekly. Other medication is not indicated except for specific indications such as antibiotics for a complicating infection should it occur.

But for serum hepatitis there is much more to the treatment than these matter-of-fact regulations. The patient often feels miserable for some days at the start and wants to be left alone, but after the fever has gone and the jaundice is well developed he has no aches or pains particularly, though he is likely to be depressed and he certainly can become bored and restless. He has no appetite, and what he tries to eat, even his usually favorite foods, just do not taste good. He needs a friend, particularly a doctor who can visualize how he feels and who has imagination and the desire to make life more pleasant for the patient. What can the doctor do along these lines?

In the first place, he can explain to the patient what his illness is all about: what has happened to the liver, why it is important to stay flat and quiet for a long time, what the landmarks are that determine so-called promotions, and all the things the patient wants to know to satisfy himself that he should be cooperative. The meals are very important in the patient's life. He would like to eat, he knows eating is good for him, but the food simply does not taste good. The doctor should not leave the food problem to the diet kitchen unless the dietitian in charge has more imagination than some. Six small meals a day are indicated, and they, of course, should be made to look appetizing. Who wants to tackle a large dish of dry cottage cheese served by itself with a spoon in mid-afternoon, or who likes an eggnog which is nothing but an egg whipped up in a glass of milk and brought in unflavored and at room temperature in mid-morning? The patient cannot have sherry in his eggnog, but at least it can be flavored with sugar and vanilla, or coffee, or tea, or be made with chocolate milk and served cold, with cracked ice if necessary. And so on through the day. Cottage cheese is good with a stewed fruit or with a salad. Crackers and a cheese spread and guava jelly kept at the bedside are a pleasant addition to a nighttime cup of hot tea. The patient's dietary whims need to be catered to. What tastes good for two or three days may pall afterward. Even a daily steak can lose its appeal.

The doctor can do much also to help the patient fight depression. He can suggest a radio or a television set, if practical. He can suggest a reading stand that will straddle the patient's body and hold a book or magazine for easy reading. Later on, as the patient improves, the doctor can drop a hint to a relative or friend to bring to the patient something the patient can do with his hands—puzzles, a sketch pad, and a charcoal pencil and eraser, even knitting or crocheting materials. A busy person does not have time to be depressed. Incidentally, an electric razor will be welcomed by most men.

But most of all, the doctor will see the patient daily, if possible, and will

try to bring in to him some bit of cheer each day from the world outside—a greeting from a mutual friend, an anecdote, or a funny story.

To many patients the doctor's visit is the one big event of the day. I recently had the pleasure of reading in the *McGill Medical Journal* a speech the late Dr. A. H. Gordon gave some thirty years ago about his own serious case of typhoid fever. He stressed the importance of the visiting doctor's sharing the patient's point of view and of his each day leaving with the patient some element of comfort and interest. Having had two hospital sessions of six weeks each, I can see what Dr. Gordon meant when he quoted this poem:

When breakfast's o'er, my bath is done,
My room is neat to see.
The event of the day takes place,
My doctor visits me.

I have a host of aches and pains
But I forget them all,
Unless as happened one dark day,
He doesn't make his call.

Thus, the sympathetic doctor will always be ready to show interest in the patient's complaints, which in a hepatitis patient will be many, unless someone, perhaps the doctor, has tipped the patient off to try to make each person who enters his room feel the better for having been there. That really works sometimes.

On a polio service we once had at the Knickerbocker Hospital in New York, there were patients who had to be told: "There are three kinds of patients on this ward: those who are liabilities, those who do not count, and those who are assets to the service. Which kind are you going to be?" And most patients proceeded to prove they were assets.

One final word, and this is about the economics of serum hepatitis or homologous serum jaundice. In at least one case a court has ruled that when accidentally or spontaneously acquired by medical or laboratory personnel, it is an occupational disease, compensable under workman's compensation laws.

Furthermore, homologous serum jaundice is listed in the *Manual of the International Statistical Classification of Diseases,* sixth revision, under the heading of "Therapeutic Misadventure in Infusion and Transfusion," under Code No. E951. "Misadventure" is a synonym for "accident." In this international list all *diseases* are listed by a number without a preceding letter, and *accidents,* poisoning, and violence have a separate chapter and are listed by a numeral preceded, as in this case, by the letter "E." This classification has been adopted officially by the United States Government, by the Army and Navy, and by all state departments of health. In my case, I have an old insurance policy which insures me for accidents only. It does not define an accident but states that the effects of the accident must be immediate in occurrence. Although it is difficult to demonstrate that the effects of a transfusion with infected blood are immediate, the company agreed to compromise my claim, evidently accepting the fact that homologous serum jaundice is an accident. This is apparently the first time that an insurance company in New York City has paid on an accident claim for post-transfusion jaundice.

Thus does one's knowledge and interest in a disease become increased by having an attack of it one's self. It is an old saying that by being a patient, every doctor can profit greatly,

if he will, by learning what it is like to be a receiver of medical attention. What at first may appear a hardship and a problem can become an opportunity.

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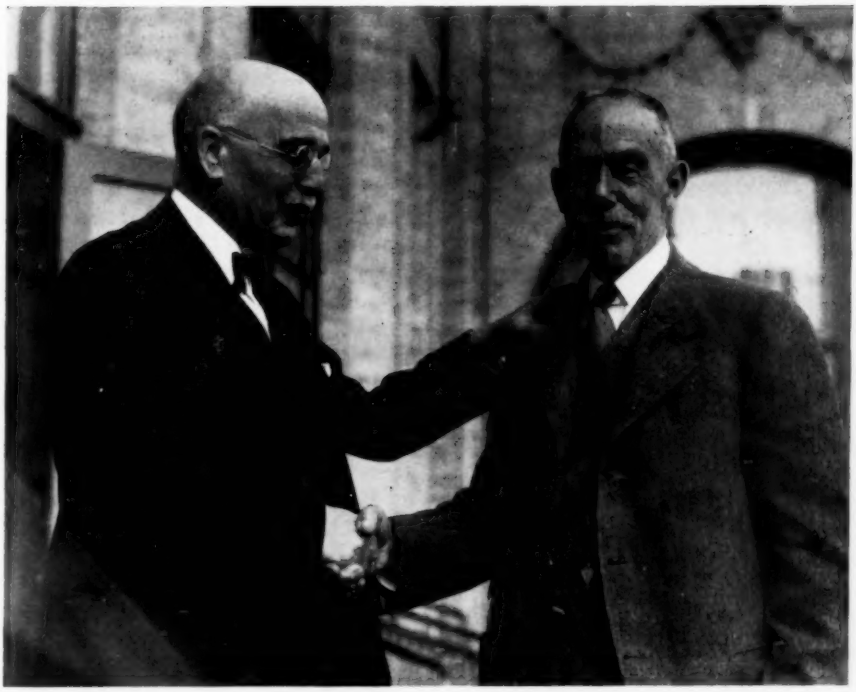
Pediatric Profiles

John Lovett Morse
(1865–1940)



Dr. Abt congratulating Dr. Morse
on his installation as president of the American Academy of Pediatrics in 1931.

JOHN LOVETT MORSE was born in Taunton, Massachusetts, of an old, well-to-do New England family. He was educated at Harvard College and at the Harvard Medical School.

About 1895 he became associated with the Children's Hospital and the Infant's Hospital, and was appointed to a teaching position under Dr. Thomas Morgan Rotch in the young and small department of pediatrics in the Harvard Medical School. He was assistant professor for several years, and when Dr. Rotch died in 1914 he was made head of the department, from which he retired in 1921—not on account of age, but because of certain disagreements in policy with the administrative authorities of the Harvard Medical School. From then until his death he devoted himself to his private consulting practice.

"Johnny"* Morse appeared on the

*He was known by this name to all American pediatricians; Mrs. Morse always called him "Johnsy." I cannot write of him as "Dr. Morse."

scene when pediatrics was just beginning to be established as a specialty. He soon had the largest and most fashionable pediatric practice in Boston, which he gave up about 1914 to confine himself exclusively to consulting practice. At the height of his career (1910 to 1921) his reputation was so high and his acquaintance among the practitioners of New England so extensive that it seemed to us who worked with him that if any sick child needed a consultation, Johnny was automatically called, and we traveled all over New England for him when he was too busy to go, or during the summer when he was away. Henry I. Bowditch (now dead), Fritz B. Talbot, Richard M. Smith, Edwin T. Wyman, and Lewis W. Hill were his assistants at various times. As a wise and common-sense consultant, Johnny was superb; parents and doctors almost always felt that they had been helped by his advice, be the prognosis good or bad. He had, to a high degree, the ability of summing up a situation in a common-sense, practical way, and he got the gist of it across to the parents without any obscurities or long-winded, long-worded "medical talk."

His knowledge of medicine was extensive, and, above all, accurate. He was a great believer in very careful physical examination, and was a master at it. He took a good deal of time in going over patients, but never dawdled. He was alert to scientific medicine, and was well up in the advances of his day, but with him the comfort and well-being of the patient came first every time, and often I have heard him speak sharply to nurses if he thought a child was not wrapped up warmly enough when brought to an amphitheater clinic, and he had a bitter tongue for students or house officers if they did not handle a patient gently. He was by no means a therapeutic nihilist, but did not use many drugs, and always with a clear purpose in view. His mind was orderly and logical to an extreme degree: he was a remarkably clear thinker, and skillful at expressing his thoughts in simple, forceful language, whether spoken or written. He was very conservative by nature, not only in medicine, but in every aspect of his life. Anything new he looked upon with suspicion until it had been proved good. When he was convinced it was good he adopted it, and let go of it with difficulty, even if it became outmoded and better things had come to take its place. This trait in his later years was intensified to such a degree that it did him harm—he was altogether too skeptical of all advances in medicine.

He excelled as a teacher. Every student was always alert and listening whenever he spoke: he had a remarkable power of holding his audience, and of bringing out the essential points in discussing any case, so that those who heard would remember. In his day a great deal of the teaching was done by amphitheater clinics. These he prepared very carefully in advance so that he knew every little detail of each case before presenting it.

He was a regular attendant for many years at the meetings of the pediatric section of the American Medical Association, the American Pediatric Society, and the American Academy of Pediatrics, and had been president of each. He was noted as a discussor of papers, and never hesitated to say

what he thought, no matter if it was unfavorable to the reader of the paper. He sometimes went too far with sarcasm or ridicule, and consequently made enemies. He was a lifelong foe of sham, insincerity, and faddism, and went after these tooth and nail, and no holds barred, wherever he thought they existed in medicine. He was not always right—he sometimes attacked things which had no evil in them simply because they were new, or he did not like the originator. He had the habit, which was very effective in discussion, of waiting until everybody had spoken, and of then getting up slowly, waiting a little while, until everybody in the hall was quiet, and then summing up with a great deal of skill, what the previous speakers had said, and often tearing it to bits. By then, the time allotted for discussion of that particular paper was about over, so he usually had the advantage of having had the last word.

He was an entirely reliable and honest man—he could be depended upon to do what he said he would do, and he expected anybody with whom he had dealings to act the same. He was never late for a lecture, a consultation, or a train: he had a very unpleasant habit of being quite disagreeable to patients who were a bit late for office appointments. Laziness, shiftlessness, carelessness, or unpunctuality he abhorred. He was very affable most of the time with those he liked, and an excellent companion and conversationalist. He loved a joke, and sometimes laughed so hard that he became purple in the face. On the other hand, he undoubtedly was pretty crotchety, sometimes a bit vindictive, and it was not easy for him to be charitable toward anyone whom he thought had injured him. He occasionally had what I used to call "ugly spells," when he could be very disagreeable. Fortunately these never lasted long. He was not what I would call a vain man, but he did take a great deal of pleasure in being praised for anything he had done, and loved to be surrounded at medical meetings, as he often was, by a group of younger admiring pediatricians.

Entirely apart from the income of his practice, which was considerable, he was a wealthy man. In spite of this, he lived simply—he was frugal, but by no means ungenerous or miserly. He respected the value of a dollar, and waste or foolish expenditure was anathema to him; I doubt if he spent more than half his income. His clothes were made by one of the most expensive tailors in Boston—but he had few clothes; his shoes were made to order, but he had few shoes; he smoked fine Havana cigars—but he had few cigars. He always had a large, expensive car, but Nelson, his chauffeur, who had been with him for many years, took such good care of it that it lasted a long time. He knew good things, and was fond of them, but he was fond of them in moderation. He was similar to many other New Englanders with inherited wealth: they do not like to throw their money around.

Johnny weighed, I would expect, about a hundred thirty pounds, and stood about five feet four. He made up for his small size by the power of his personality. We used to call him "our little fighting cock." He wrote clear, vigorous English, and knew very well the construction of the lan-

guage, but of literature and art he knew little and cared less. He was not a voracious reader, and when he did read, *The Saturday Evening Post, Collier's,* or one of the Wall Street financial magazines was about as far as he got.

He took considerable pleasure in looking after his money, and spent a good deal of time at it. Each investment was catalogued in a card index, and although he had a large capital, only a small amount was invested in any one security, in order to provide safety. He was constantly changing his investments in order to meet changed business conditions, and was at his broker's frequently, but I doubt if he ever bought a share of stock on margin. He did not try to make money in the boom of 1929: the depression of 1932 affected him not at all. He would have made a superb bank president.

He was devoted to his wife, who was an unusually gracious and attractive woman, of very calm and even disposition. He had much respect for her judgment, and paid a great deal of attention to it when he had to make decisions of any sort. For many years Johnny, Mrs. Morse, and their boy Lovett went for two months in the summer to a small, rather old-fashioned inn, "Philbrook Farm," in Shelburne, New Hampshire. His chief amusements here were golf, tennis, and trout fishing. Johnny married rather late, and before his marriage moose hunting was his chief diversion, and he had shot seventeen moose to his own gun. At the old University Club, on Beacon Street, he had also been a formidable poker player. At Wayland, about twenty miles from Boston, he had a small old-fashioned farmhouse in a most attractive setting. For many years he went out there every week end, leaving one of us to attend to any business that might turn up at home. This break in routine was necessary for him, because he was not only head of a large (for that time) pediatric department and hospital service, but also had a really large consultation practice, and his days were full. When he was professor of pediatrics, at which he certainly spent half of his time, his salary was $1,800 a year. The next highest paid man in the department got $600, and the budget for all purposes was $4,000.

Johnny's fee for an office consultation was $20.00; for a house consultation in Boston, $25.00—for places like Lowell, New Bedford, or Worcester, $100.00, or possibly somewhat more if the family was wealthy. When he had patients in the private ward of the hospital his fees were based upon what he thought his services were worth to that particular patient, rather than a set fee for daily visits. The largest fee I ever knew him to charge in Boston was $500 to a wealthy family from a distance whose baby, aged about one year, was in the hospital for only a few days. The baby had a unilateral exophthalmos of such degree that the eye was practically hanging out of his head. The parents were beside themselves, as they had been able to find nobody in their own state who knew what the matter was, or how to get the eye back where it belonged. Johnny had it back in short order by the liberal use of orange juice. The parents paid the fee without a murmur, and went home happy. Afterward in discussing the case with Johnny I said I thought

he had charged them a pretty stiff fee for such a small amount of work and such a short stay in the hospital. "Not at all," said he, "where would the baby be if it hadn't been for somebody like me who knew all the unusual manifestations of scurvy? They got their money's worth, and more, too."

Johnny was a profuse writer—he wrote about 275 papers, and several books. His papers at the time they were written were very much worth while—although he realized the value of keeping his name before the medical public, and I suspect wrote so profusely with this certainly as a part consideration, his papers were never what I would call "pot boilers." He always had something to say which was worth reading, and he wrote on almost every conceivable subject that had to do with pediatrics. His books had a brief vogue, as most medical books do, and are now forgotten, although his large textbook of pediatrics, written about 1923, has many things in it which are well worth consideration by even the most modern and up-to-date young pediatrician. In his day a good pediatrician was supposed to know all that anybody knew about children; pediatrics was not then divided up into pediatric neurology, cardiology, allergy, psychiatry, and so on, as it is today, when it is quite impossible for any one pediatrician to be expert in all these fields. Johnny was expert in almost all parts of pediatrics as it was known in his day. He was particularly good at neurology, contagious diseases, and anything to do with the heart and lungs. He always had a ready answer for almost any question concerning pediatrics that one could ask. I commented on this to him once and said, "How do you possibly remember so much about so many things?" Honest John said, "I don't remember, I look in the book the same as any medical student does."

Almost all of Johnny's contemporaries are dead—the youngest of his former house officers is 60; those of his former assistants who are still alive are older than that. When any of us get together occasionally at medical meetings or elsewhere, the talk sooner or later turns to Johnny Morse, his virtues and vices, his many little foibles, peculiarities and idiosyncrasies, and his influence upon us when we were young fry—for his personality was such that his influence was profound. He was a unique character, with many facets, and in spite of the reputation he had for being peppery and sometimes difficult, a very human one and a lovable one to those who knew him well.

Lewis Webb Hill

Comments on Current Literature

NONSPHEROCYTIC HEMOLYTIC DISEASE

WITHIN recent years continued developments in the field of hematology, particularly with reference to improved laboratory methods, have resulted in the recognition of clinical hematologic entities, and have aided in their more efficient classification. By engendering better understanding of the factors involved, these developments have contributed to more rational therapy.

In the August, 1954, issue of *Blood, The Journal of Hematology*, Motulsky, Crosby and Rappaport[1] report investigations concerned with a "singular familial hemolytic syndrome," a condition designated as hereditary nonspherocytic hemolytic disease.[2] This presentation is based on detailed investigations of four patients from three unrelated kindreds who were studied thoroughly at the Army Medical Service Graduate School, the Walter Reed Army Medical Center, and the Armed Forces Institute of Pathology in Washington.

In addition to the usual clinical and hematologic examinations, the authors were able to undertake in these patients special studies of iron metabolism, red cell survival, osmotic and mechanical fragility after incubation, search for abnormal hemoglobin, and a study of histologic features in spleen and liver biopsy specimens. All four of these patients, two of whom were mother and infant, presented findings which were interpreted as criteria of hemolytic anemia; erythroid hyperplasia of the bone marrow, reticulocytosis, hyperbilirubinemia, increased fecal urobilinogen, and rapid turnover of tracer iron in the plasma. Additional features of the clinical entity described included anemia, jaundice, and splenomegaly with no consistent abnormal morphology of the red cells.

Since difficulties may be encountered in differentiating this syndrome from other hematologic entities, the authors offer several practical suggestions which may aid the clinician in differential diagnosis. In their patients, fresh blood specimens under cover slips showed normal cell thickness and normal rouleaux formation, and the authors found this simple test one of the best means of differentiating hereditary nonspherocytic hemolytic disease from hereditary spherocytosis in which similar fresh blood specimens show thick spherocytes forming irregular and uneven rouleaux. Studies carried out on these four patients indicated that osmotic and mechanical fragility of the red cells was essentially normal. These results are in striking contrast with those obtained for spherocytic cells which show increased osmotic and mechanical fragility, particularly after incubation for twenty-four hours at 37° C. Red cell survival time was investigated in two of the four patients. Normal cells transfused into these patients had a life span within normal limits for washed red cells. When cells from one of these patients were transfused into a normal recipient, the mean life of the donor cells was thirteen days. In the other of these two patients the donor's red cells were tagged with chromium-51 and returned to his own circulation. Their mean life span was seventeen days. The decrease in survival time shown by these cross-determination erythrocyte studies is considered by the authors to be characteristic in all

hemolytic anemias which are associated with an intrinsic defect of the red cells causing their premature disintegration.

The hereditary pattern in these families and in those reported to date in the literature suggests basic transmission according to autosomal dominance, the gene, or genes, responsible for the condition apparently having low penetrance, and varying considerably in expression in the individual family member. In consequence when the family study is negative, the diagnosis may be difficult. However, since, as a rule, many factors are operative in human genetotropic disease, further analysis of affected families is necessary before the condition can be classified as to its hereditary progression.

Motulsky and associates discuss differential diagnosis and therapy at some length, listing a number of conditions to be ruled out. When nonspherocytic hemolytic disease is present at birth, or is manifest very early in life, confusion with erythroblastosis fetalis is possible. Appropriate tests will usually serve to distinguish between these conditions. Hereditary spherocytosis and Cooley's anemia rarely show marked manifestations at birth. However, differentiation between very early manifestations of nonspherocytic hemolytic disease and those of hemolytic disease of the newborn due to ABO incompatibility may be difficult, since the Coombs test is often negative in the latter.

According to the authors, confusion would be most likely to occur between hereditary nonspherocytosis and hereditary spherocytosis. This differential diagnosis is of considerable importance since in the latter, splenectomy has given excellent results even in mild cases, while in nonspherocytic hemolytic disease, splenectomy has been of little or no value. With some exceptions, the "presence of microspherocytes, the characteristic deformed rouleaux pattern, increased osmotic, mechanical and oxalate fragility clearly differentiate hereditary spherocytosis from hereditary nonspherocytic hemolytic disease." The differential response to splenectomy in these two conditions is borne out further by studies of the splenic pulp which in hereditary spherocytosis is markedly congested with spherocytes, in this condition the spleen being the only tissue selectively retaining and destroying spherocytes. Removal of the spleen allows spherocytes to survive a normal life span, and the hemolytic process is alleviated. By contrast, in cases of nonspherocytic hemolytic disease, the splenic pulp shows no congestion, and even after splenectomy has been performed, erythrocytes continue to be destroyed prematurely. Thus, in general, splenectomy is not indicated or advocated in the nonspherocytic hemolytic condition. The authors point out, however, that in certain severe cases it may be indicated, particularly in patients with splenomegaly who have thrombocytopenia, leukopenia, and extracorpuscular hemolytic disease superimposed upon the intrinsic red cell defect.

From a pediatric point of view, it is of interest that Case 1 of the authors' series was a male infant, 2 days of age, whose original diagnosis was erythroblastosis fetalis. In spite of exchange transfusion with temporary favorable response, the patient still showed a moderately severe hemolytic process at the age of 3 months. At 10 months of age splenectomy was performed, and while the patient recovered from the operative procedure with no difficulty, the intensity of the hemolytic process did not diminish during a period of eighteen months following surgery. In this infant with neonatal jaundice suggesting erythroblastosis fetalis, the Coombs test was negative, and no ABO or Rh incompatibility between mother and infant could be demonstrated.

In summary, the authors point out that in all probability further study of hemoglobin irregularities and of erythrocyte morphology and physiology will define more clearly the red cell defect responsible for hereditary

nonspherocytic hemolytic disease. Until such clarification is possible concerning the various factors involved in shortening the life span of the affected erythrocytes, it seems reasonable to suggest that "any inherited hemolytic syndrome not associated with a characteristic anomaly of red cell shape must necessarily be classified as hereditary nonspherocytic hemolytic disease."

RUSSELL J. BLATTNER

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Correspondence

Letter to the Editor:

My manuscript that was published in the October issue of THE JOURNAL OF PEDIATRICS was submitted to the Editorial Board as a summary of the treatment I thought was best at the present time in the processing of the newborn infant requiring oxygenation. It is a method with a minimal amount of handling or treating on the part of the physician or nurse. The manuscript was offered by me for publication following the proposal of the Editorial Board that the important controversial subject it covered would be discussed by physiologists, pathologists, obstetricians, and pediatricians, and that discussion appear in all reprints. The reader easily can see that it settled into a controversy centering almost entirely about the Bloxsom Air Lock, and not about the best way of processing the handicapped newborn infant in an effort to lower neonatal infant mortality, a problem which certainly merits the best efforts of all physicians.

Two of the discussants object to my statement, "The ordinary means of resuscitation, as pointed out by Best and Taylor, are bound in advance to fail because of partial inadequate expansion or nonexpansion of the fetal lung," one claiming it, "is thoroughly wrong," and the other, "This sweeping statement is misleading, unless it means that a degree of nonexpansion is sometimes reached at which various resuscitative measures are useless." For the benefit of the reader, I quote in full from the paragraph from Best and Taylor on page 358 of the Fifth Edition of *The Physiological Basis of Medical Practice* their remarks about "methods of resuscitation."

"*Resuscitation of the newborn.* Asphyxia in the newborn infant is usually due to the failure of the lungs to expand fully, alveoli in areas of the pulmonary tissue remaining in the fetal state (atelectasis). The methods of resuscitation which may be effective in the adult are likely to fail. Cutaneous stimulation, e.g., slapping, hot or cold water, are time honored devices which are usually ineffective. The object aimed at should be the expansion of the collapsed alveoli." The reader can now judge as to whether my statement is "thoroughly wrong" or "misleading."

The Bloxsom Air Lock has now been in clinical use four and one-half years. Since my original publications in 1950, only two succeeding papers have appeared on this lock. The first paper was published by Drs. Virginia Apgar and Joseph Kreiselman, entitled "Studies on Resuscitation. An Experimental Evaluation of the Bloxsom Air Lock" which appeared on pages 45 to 53 of *American Journal of Obstetrics and Gynecology* of January, 1953. The second paper was published by Sister Mary Angelique and myself, entitled "Neonatal Infant Mortality. Before and After the Use of the Air Lock for the Treatment of Newborn Infants in a Large Maternity Hospital," and appeared in *American Journal of Obstetrics and Gynecology* of March, 1954, pages 647 to 650.

Question.—Do you think that it is a little strange that if this device was of no value, that during four and one-half years following its introduction, a number of manuscripts would not have appeared in the medical literature attesting to its worthlessness?

For the reader to make his own evaluation of the Bloxsom Air Lock, the summaries of the above papers are given in full with pertinent questions. The paper by Drs. Apgar and Kreiselman contains three conclusions; I am quoting in full, and the reader is asked to form his own opinion.

Summary of the Publication by Drs. Apgar and Kreiselman

1. In adult dogs in which hypoventilation was produced by drug depression, oxygenation and removal of carbon dioxide proceeded satisfactorily in the Bloxsom Air Lock, in an atmosphere of 58 per cent oxygen at pressures varying between 810 and 910 mm. Hg, at a cycle of 38 and 5 seconds.

Question.—If you had an infant that you clinically thought had hypoventilation due to drug depression, would you, in an effort to aid that infant, treat him in an Air Lock in view of this experimental study?

2. In adult dogs made apneic by drug depression, the Bloxsom Air Lock was unsuccessful in all cases in oxygenating the animals and removing carbon dioxide.

Question.—Has Bloxsom ever stated that an apneic dog from drug depression would be oxygenated and be freed of carbon dioxide by treatment in the Bloxsom Air Lock or that the Air Lock was a miracle device that would oxygenate all apneic infants?

3. An analysis was made of other suggested advantages of the Air Lock. They appear to be unsubstantiated in respect to removal of fluid from the lungs, and absorption of oxygen by the skin.

Question.—Would you be willing to read the entire article by Drs. Virginia Apgar and Joseph Kreiselman and determine for yourself whether or not they did any experimental work with newborn animals to justify this conclusion?

The Publication by Dr. Bloxsom and Sister Angelique

The paper by Allan Bloxsom and Sister Mary Angelique contains four conclusions; I am quoting in full, and the reader is asked to form his own opinion with regard to them.

1. The reduction in the forty-eight-hour neonatal death rate in 1952 in the St. Joseph's Maternity Hospital has exceeded considerably the original optimistic report.

Question.—Is the above true from the original published reports?

2. There has occurred a reduction in the forty-eight-hour neonatal death rate of the term infant in the St. Joseph's Maternity Hospital in Houston from 63 per 10,000 term deliveries in 1949 to 37 per 10,000 term deliveries in 1952 because of early and rapid oxygenation to establish respiration. This is a reduction of 41 per cent and represents a salvage of 26 infants from a former loss of 63 term infants.

Question.—Knowing that there have been no changes in nursing hours available per patient, medical resident hours available per patient, epidemics of Salmonella or other infections, and method of handling, so far as can be determined in this hospital between 1949 and 1952, except the use of the Air Lock in 1952, would you believe the reduction in that mortality was due to the use of the Air Lock?

3. There has occurred a reduction in the forty-eight-hour neonatal death rate of the premature infant in the St. Joseph's Maternity Hospital in Houston from 2,228 deaths per 10,000 premature deliveries in 1949, to 1,504 deaths per 10,000 premature deliveries in 1952, a reduction of 32.5 per cent. This represents a salvaging of 724 premature infants from a former loss of 2,228 premature infants per 10,000 infant deliveries.

Question.—Knowing that there has been no changes in nursing hours available per patient, medical resident hours available per patient, epidemics of Salmonella, or other infections, methods of handling that are no different between 1949 and 1952, so far as can be determined, except the use of the Air Lock in 1952, would you be influenced by the chi square values as computed by Dr. Weech?

(*Note:* Dr. Weech states in regard to the mortality figures for the term infant in this hospital in 1949 and 1952, "The odds that the results of 1952 are different from those in 1949 are about 19 out of 20. Stated the other way, the chances are 1 in 20 that the difference in fatality rates is purely fortuitous." For the premature infant mortality rate reduction of 1952 as compared with 1949, Dr. Weech states, "The odds are, therefore, less than 1 in 100 that this difference could have resulted from fortuitous circumstances alone.")

4. The primary causes for this reduction are believed at the present time to be (a) the rapid oxygenation of the anoxic infant by the Air Lock and (b) an increased rate of metamorphosis of the low cuboidal cells lining the alveolar sacs brought about by pressure changes in the Air Lock whereby these cells change to a flattened type causing an increased efficiency of the lungs through providing a greater surface of the cells lining the alveolar sacs for the exchange of oxygen and carbon dioxide.

Question.—Would you be willing to read the entire paper by Bloxsom and Angelique if you believe the explanation is faulty and form your own opinion as to the reasons for the reduction in term and premature infant neonatal mortality in that hospital in 1952 as compared with 1949?

The individual reader now has the value of findings in the experimental animal hypo-

ventilated by drug depression in which oxygenation and removal of carbon dioxide proceeded satisfactorily with cycling in the Bloxsom Air Lock. He knows the Air Lock is not a barospirator to keep animals or infants alive indefinitely. He also has available chi square values with regard to mortality rates of term infants and premature infants of some 12,449 infants, which chi square values show (1) the chances are only 1 in 20 that the difference in fatality rates is purely fortuitous for the term infant between 1952 and 1949, and (2) less than 1 in 100 that this difference could have resulted from fortuitous circumstances alone in the premature mortality reduction. Stated differently, the chances are 19 in 20 that the reduction is a real one for the term infant. I should point out, however, that the comparison of results in one year with those in another is always hazardous as has been pointed out by Dr. Weech. The reader can and should form his individual opinion from what is definitely known about the Air Lock.

If obstetricians, pediatricians, anesthetists, and pathologists do nothing more than meet and review again and again the known facts that influence perinatal mortality, more infants will be helped over this emergency and the neonatal mortality rate will be lowered in their community. A fresh start is certainly in order in every locality.

ALLAN BLOXSOM

News and Notes

Dr. William C. Adams was appointed to the full-time faculty of the University of Louisville as instructor in Child Health. Dr. Adams was graduated from Temple University School of Medicine in 1947, and received his pediatric training at the University of Illinois and at Temple University.

Dr. Benjamin Morris Gasul has been appointed chairman of the Department of Pediatrics of Presbyterian Hospital in Chicago. Dr. Gasul succeeds Dr. Heyworth N. Sanford.

Dr. M. G. Peterman delivered a lecture on the Convulsive Disorders of Childhood at the University of Amsterdam in Holland on September 15.

The annual pediatric postgraduate refresher course at Tulane this year will be devoted to "Pediatric Therapeutics"; Dr. Henry G. Poncher will be the guest speaker. The program will be under the direction of Dr. Ralph V. Platou and will last from Monday, Feb. 7, 1955, at 8:30 A.M. through Friday noon, Feb. 11, 1955. Specific therapeutic approaches for a wide variety of pediatric problems will be considered, with many members of the faculty participating. Registration will be limited to forty qualified specialists in pediatrics. Those interested should contact Dr. C. G. Grulee, Jr., Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12, La.

Book Reviews

Textbook of Pediatrics, ed. 6. Edited by Waldo E. Nelson, M.D., Philadelphia, 1954, W. B. Saunders Co., 1,581 pages. Price $15.00.

The sixth edition of "Griffith," "Griffith-Mitchell," "Mitchell-Nelson," now quite properly becomes "Nelson." Since the first edition appeared in 1933, the textbook, ably edited in turn by Mitchell and by Nelson, has established itself as one of the standard pediatric texts in English. In the preface to this edition the editor simply notes that some sections have been rewritten and new ones added. In all, we note seventy well-known pediatricians who have contributed to this edition, and a comparison with the fifth, published in 1950, discloses a number of changes in authorship and the addition of new names. A number of chapters have been rewritten, including the newborn, cardiovascular disease, the blood, endocrine disease, and tumors, and despite the inclusion of new material, by careful editing and rewriting, the size has been reduced about seventy-five pages. Of the new material, cat-scratch fever, cytomegalic inclusion disease, and kwashiorkor are included, we believe, for the first time in a pediatric textbook. Many of the illustrations are new and the number slightly increased.

While it is impossible to review an established textbook of this nature in detail, enough has been mentioned to point out that the new edition is not a reprint, but a carefully revised text that has kept pace with the advances in pediatrics which have been made in the last four years.

Illustrated Handbook of Child Care From Birth to Six Years. Wava McCullough assisted by Marcella Gawronski, R.N., New York, 1954, McGraw-Hill Book Co., 232 pages. Price $3.00.

With the scores of books published on child care, it is unusual to find something that is really new and useful as well as attractive. The author is not only a clever artist but experienced in educational writing. The text consists of over 400 attractive drawings with legends, telling and explaining how to care for the child, and illustrating the child's development. A good picture of just how to carry out a procedure is worth hundreds of words of text to the inexperienced mother. Dr. Arthur Parmelee writes a brief foreword, and the mere fact that he has checked the illustrations page by page for the book gives assurance as to the accuracy and soundness of the text and illustrations. This application of the principles of visual education to a book on child care is a distinct advance in a field that has been oversupplied in recent years with a number of books which rated about the same. It is one that can be particularly recommended to the young mother with her first baby.

The Normal Child. Ronald S. Illingworth, M.D., F.R.C.P.(Lond.), Boston, 1953, Little, Brown and Company, 342 pages. Price $6.00.

This text by the professor of child health at the University of Sheffield covers the first three years of life. The text, which is based on the anatomy and physiology of these developing years, does not go into the question of disease, but is concerned with the "problems" that arise during the period and which the practitioner frequently meets in his work. These he divides into four groups which make up the sections of the book: Feeding, Physical, Developmental, and Behavior. While there is overlapping in the four divisions, as, for example, behavior problems occur in children with developmental problems, it makes a satisfactory method of presentation and in many ways preferable to the chronological method of presentation. The discussion is clear and not exhaustive, and there is extensive reference to the work and writings of others in all parts of the world. It is a good, practical book for the practitioner—particularly in his early years—who finds himself confronted with many problems that were not encountered in his hospital training which was centered on "disease." These are the problems which keep the telephone ringing.

Editor's Column

PEDIATRIC PROFILES

BEGINNING with this issue, the JOURNAL plans to publish a series of "Pediatric Profiles." They will appear from time to time, and the purpose is to present a rather personal and intimate picture of men who either by their leadership or scientific attainments have taken an important part in the development of pediatrics in the United States. No living pediatricians will be included, nor will the order of presentation in any way reflect the matter of relative importance. The editorial problem of finding someone who had a close acquaintanceship with some of the men in the list of names drawn up by the Editorial Board has not as yet been solved.

PYRIDOXINE DEFICIENCY IN INFANTS

DURING the latter months of 1952 reports began to appear of a convulsive disorder in young infants associated with general irritability, easy startling, colic, abdominal distention, vomiting, and diarrhea.[1] The convulsions usually began at 2 or 3 months but they were occasionally observed earlier, in one instance at 2 weeks of age. A moderate elevation of the spinal fluid protein, in some instances up to 100 mg., was present in most cases.

It soon became apparent that the symptoms occurred only in infants fed liquid S-M-A, and that prompt subsidence followed change of formula. Later it was found that an injection of pyridoxine would relieve the convulsions while the infant was receiving liquid S-M-A and that no further convulsions occurred if pyridoxine was added to the formula. Coursin[1b] was able to show, in a 2½-month-old infant in status epilepticus whose brain wave pattern was being followed by continuous electroencephalogram, that the intravenous injection of saline and 100 mg. pyridoxine induced sleep in three minutes and produced a normal brain wave pattern.

Pyridoxine (vitamin B_6) was first described as a member of the B group by György[2] in 1934. It was synthesized by Harris and Folkers[3] in 1939. Actually B_6 is now known to occur in nature in three forms, pyridoxine, pyridoxal, and pyridoxamine. All three are found in varying proportions in liver, meat, fish, molasses, legumes, whole wheat, and cabbage.

Vitamin B_6 is intimately concerned with amino acid metabolism. It is necessary for the synthesis of tryptophan and for its complete metabolism.[4] Pyridoxine acts as a coenzyme for the enzyme that removes the carboxyl group from many of the amino acids. The B_6 group is also essential for activating the transamination reactions of amino acids.

Vitamin B_6 participates in many phases of fat metabolism—its transport, oxidation, synthesis, and deposition. It seems to be particularly con-

cerned with the metabolism of the unsaturated fatty acids. When the supply of vitamin B_6 is deficient, fat stores are rapidly depleted.

Various animals deprived of vitamin B_6, show fairly well-defined symptoms referable to the skin, the nervous system, and the blood. Weeping scaly dermatitis with localized edema; convulsions, ataxia, muscle weakness, and leg paralysis; hypochromic, microcytic anemia, and a decrease in the number of lymphocytes have been reported by different investigators.

Pyridoxine has been used in the treatment of many conditions—cheilosis, epilepsy, Parkinsonism, progressive muscular dystrophy, various skin diseases—but its clinical value in these is doubtful. It has been used widely in the treatment of nausea and vomiting of pregnancy, but a carefully controlled study by Hesseltine[5] failed to establish its value. It appears to benefit the symptoms of radiation sickness.

In 1953 Snyderman and associates[6] reported a study of long-term deprivation of pyridoxine in two male infants, 2 and 8 months old, respectively. The earliest clinical change observed was a failure to gain weight. This began in the younger infant after thirty-three days on the experimental diet, in the older one after seventy-three days. On the seventy-sixth day the younger infant, following a four-day period of listlessness, apathy, and anorexia, suffered a series of severe convulsions after which he lapsed into coma. He was given an intravenous injection of 50 mg. of pyridoxine hydrochloride and three hours later he began to improve. By the next day he had reverted to his former state. The older infant showed no convulsions but developed a microcytic, hypochromic anemia which responded promptly to pyridoxine administration.

The authors concluded that pyridoxine in infants is necessary for growth, for red blood cell formation, and for maintaining the integrity of the central nervous system.

An infant with severe convulsions, who responded in an extraordinary manner to the administration of pyridoxine, was reported by Hunt and co-workers.[7] The infant was the third child of a seemingly healthy mother, 31 years old. The first-born child, 6 years of age, was well. The second child, born eighteen months prior to the birth of the patient, began convulsing four hours after birth and succumbed within thirty hours. Autopsy was negative. During the second and third pregnancies the mother had received intramuscular injections of pyridoxine hydrochloride and thiamine hydrochloride in an effort to control nausea and vomiting.

The weight of the patient at birth was 3.2 kg. Three hours after a normal delivery generalized twitchings appeared. Five days later severe convulsions took place. The serum calcium was normal and no response followed calcium gluconate, Sodium Amytal, and magnesium sulfate. The convulsions recurred at frequent intervals during the hospital stay.

Investigation revealed that the infant's convulsions could be controlled by pyridoxine, and that pyridoxine was capable of altering the grossly abnormal electroencephalogram. It was found, further, that a daily require-

ment of 2 mg. of pyridoxine hydrochloride was necessary to prevent convulsions. This is several times the probable requirement for normal children (less than 0.15 mg. daily) and indicates an inborn metabolic defect. When last seen at 23 months of age, the child's physical development was normal but mental development was retarded markedly.

The occurrence of convulsions in infants fed a proprietary preparation of milk has led to the discovery of a new vitamin deficiency disease. This chance event promises to open up new fields of study for the pediatric investigator.

H. B.

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REFLECTIONS ON THE NEWCASTLE INQUIRY

IN AUGUST a book was published which should be compulsory reading for those with the responsibility for pediatric education in the United States, and it deserves careful study by public health officials and pediatricians who are interested in the health and medical care of children. It bears the title, *A Thousand Families in Newcastle Upon Tyne*,* and the authors are the late Sir James Spence and his associates, Drs. W. S. Walton, F. J. W. Miller, and S. D. M. Court.

The book reports on the findings for the first year of life of an inquiry or study that is being continued over the early years of childhood "designed to identify the diseases of childhood in a representative group of families, to trace their origins, and to measure their effect."

The material on which the report is based was the enrollment in May and June, 1947, of all infants born in Newcastle, in all, 1,142. Of these, 44 died in their first year, 127 moved from the city, and 4 left the survey, leaving 967 in the group at the end of the first year. The study group was made up of pediatricians and experienced health visitors who acted as observers and recorders, but did not take part in the medical care and treatment of the infants. By taking all births in the two-month period, the enrollment gives a picture of what occurred to infants born to parents in all social and economic classes, and reared in housing conditions varying from excellent to those considered unfit for habitation. Thus the material is adequate to meet the purpose of the study "to measure the frequency and extent of disease and disablement in a representative sample

*A Thousand Families in Newcastle Upon Tyne, Oxford University Press, 114 Fifth Ave., New York, 217 pages. Price $3.00.

of the city's children. . . ." We know of no other study so broad or extensive in scope. Most unusual was the support and cooperation given to the study by the families, and by the medical practitioners who attended the families.

Of the 967 infants, 203 had no recorded illness during their first year. The remaining 764 had a total of 1,625 illnesses. Of these, 57 per cent were respiratory: 1 in 5 had bronchitis, 1 in 10 whooping cough, 1 in 14 otorrhea, and 1 in 20 pneumonia. In twenty families there was an "entrenched staphylococcus infection" which caused surface infections in the infants but no serious illness. Four out of five of the infants had significant illnesses during the year requiring medical attention. This was given in 905 of 1,153 illnesses by the family doctor. On thirty occasions he sent the child for admission to a hospital and on ninety-two to an outpatient clinic. Thus in Newcastle the family doctor carried the chief responsibility for the diagnosis and treatment of the illness. Only eighteen "uncommon but significant" diseases were recorded for 1,011 infants, including pyloric stenosis 3, acute intussusception 4, meningitis 4, and pink disease 5.

The text and appendix contain numerous tables and statistics showing such relationships as illness and medical care to "social classes" and housing, the extent and duration of breast feeding, the extent of prematurity, illegitimacy, accidents, and of many other details which were recorded.

Much attention was given to evaluating the maternal care. For 80 per cent of the infants this was regarded as satisfactory and for 14 per cent unsatisfactory. The authors reached the conclusion that the capacity of the mother was the determining factor in how the infant fared. To quote, "If she failed her children suffered. If she coped with life skilfully and pluckily, she was a safeguard of their health . . . our experience confirms that in all sections of society she remains the chief guardian of child welfare, a fact which is sometimes in danger of being forgotten . . . rarely can a family survive if the mother fails." This finding, that maternal capacity emerged as the chief single factor in the welfare of the infants, is all the more arresting when one studies the tables in the report showing the large amount of bad housing and tremendous overcrowding which made up the physical environment in which so many of the infants spent their first year of life.

The importance and significance of the study lies not only in the wealth of factual material it contains in regard to the health of the infant during his first year, but in the author's interpretation of the findings in their relationship to medical practice and education. While in many respects conditions and customs of medical practice are quite different in an English city when a comparison is made with the situation in an American city, and hence the conclusions and suggestions must be evaluated with this in mind, nevertheless there are some interpretations and suggestions that should be thoughtfully considered by our medical educators.

The conclusion is reached that from the standpoint of medical care a "family approach" is best. The argument for this is that infection

dominates the picture of illness in the first year of life, and this was found to be almost always an expression of family infection. For this reason they reject the view, "which is growing in the United States, that the home care of children should be in the hands of separate paediatric practitioners." This implies they feel a "family" doctor is better able to cope with the picture of family infection. While not stated so specifically, we infer the authors have prevention in mind as well as treatment. While conditions and customs of pediatric and medical practice are different in England, as was recently so fairly and ably discussed by Edwards Park,* we cannot help but feel that with the size of the "panel" the general practitioner has to carry in England, this is somewhat of a Utopian wish or thought.

Despite the fact that in Great Britain there have been a number of men who have made outstanding contributions to pediatrics—names such as Still, Hutchison, Parsons, and Findlay flash across the mind—pediatrics from the standpoint of medical education is at about the stage of development it was in the United States some thirty or more years ago. Quite logically and correctly the importance of practical clinical training in pediatrics for the general practitioner is stressed. It is the flatfooted rejection by these able and neutral observers of the "pediatric practitioner," which has been a unique contribution of pediatric development in the United States, that calls for a serious "stock-taking" on our part. The question of pediatric research is only indirectly involved. The question is rather one of the educational method by which good medical care can best be furnished for all children.

As a matter of fact there has been considerable informal "off record" discussion among pediatric leaders in the United States in the last two or three years, as to whether or not pediatric specialization in this country has gone so far that while unusually good pediatric care is available for many children, for the majority it is not as good as it should be. The rapid development of the seventy-odd university pediatric departments, with their associated children's hospital services, has tended to place emphasis on research rather than on turning out practitioners with a good pediatric training. Which function is primary is a moot question in some minds. That research has added materially to our understanding and knowledge of disease cannot be questioned. Regardless of this question the pediatric clinics have been and are turning out hundreds of pediatric specialists each year. Only a limited few of these will enter on an academic career, and the vast majority will go into the private practice of pediatrics. The training of the two, and the examination required by the "Board," is the same for both, although there is a distinct parting of the ways so far as their future functions and activities are concerned. The pediatric practitioner will enter a field in which he may never, or only rarely, encounter the types of disease or kind of illnesses upon which most of his resident training has been based. The tendency to an increasing participation by the resident in outpatient work as a part of his training is a recognition of this defect in the edu-

*Pediatrics 14: 153, Aug., 1954.

cational program for the man, who, as a specialist, enters private practice.

Perhaps the most questionable result of this development is the almost complete utilization of the children's hospitals to train specialists. This has deprived large numbers of young physicians who enter general practice of any practical hospital training by means of short-term internships, with the result they enter private practice in which a large part of their work will be with children, with only an undergraduate experience or exposure to pediatrics. Spence and his associates take the view that as most of the children in the community will be under the care of the general practitioner—a situation which the Academy survey showed exists in the United States—medical education, so far as pediatrics is concerned, should be directed to training or educating the future general practitioner, rather than turning out "pediatric practitioners" as has been the development in this country.

There is much that can be said pro and con, and it is a topic that should be discussed and considered from a broad standpoint, rather than one of research organization and administrative expediency.

We look forward to the future reports of the Newcastle inquiry, with the expectation they will be as "meaty" as this one reporting on the first year of life.

B. S. V.